Diagnostic value of $^{201}$Tl–single-photon emission computerized tomography studies in cases of posterior fossa hemangioblastomas

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Object. The $^{201}$Tl uptake index was evaluated for its usefulness in formulating a diagnosis of hemangioblastoma. Thallium-201–single-photon emission computerized tomography (SPECT) studies were performed in nine patients harboring hemangioblastomas in the posterior fossa and in five patients (six lesions) with gliomas in the posterior fossa.

Methods. The $^{201}$Tl uptake index was defined as the ratio of mean counts of isotope per pixel in the tumor to mean counts of isotope per pixel in the homologous region of the healthy brain. The $^{201}$Tl uptake indices of the early image ($T_{le}$) and that of the delayed image ($T_{ld}$) were calculated. The isotope retention index (RI) was calculated as ($T_{le} - T_{lo}$)/$T_{le}$. The $T_{le}$ was $2.7 \pm 0.7$ in hemangioblastomas and $2.9 \pm 1.7$ in gliomas (mean ± standard deviation). The $T_{lo}$ was $1.5 \pm 0.4$ in hemangioblastomas and $2.4 \pm 1.6$ in gliomas. There were no significant differences between hemangioblastomas and gliomas when $T_{le}$ and $T_{lo}$ were compared. The isotope RI was $0.43 \pm 0.07$ in hemangioblastomas and $0.15 \pm 0.1$ in gliomas, showing a significantly higher RI in hemangioblastomas compared with gliomas ($p < 0.01$).

Conclusions. Thallium-201 washout is significantly faster in hemangioblastomas. Hemangioblastoma is biologically benign, but contains a rich capillary network that forms a hypervascular tumor bed. Variations in its appearance on magnetic resonance images may cause difficulties in the differential diagnosis of hemangioblastoma. Thallium-201 SPECT studies can be used to distinguish hemangioblastomas from gliomas in the posterior fossa.

KEY WORDS • hemangioblastoma • thallium-201 • single-photon emission computerized tomography • retention index

Hemangioblastoma is a biologically benign tumor (WHO Grade I)$^{9}$ and is one of the most common neoplasms located in the posterior fossa. Hemangioblastoma displays no typical neuroimaging characteristics, although angiographic studies may show hypervascularity and MR images typically reveal a cyst with a small enhanced tumor nodule; occasionally, a huge enhanced mass resembling gliomas or metastatic brain tumors can be observed. Hemangioblastomas, in contrast with high-grade gliomas or metastatic tumors, can be cured by total resection. Therefore, a correct preoperative diagnosis may have a significant impact on therapeutic strategy.

Thallium-201 imaging, first introduced for myocardial imaging, was incidentally found to reveal isotope uptake by lung carcinomas.$^{16}$ Thallium-201 SPECT studies may be useful for the evaluation of brain tumors.$^{1,7,10,11,13,14,18}$ The $^{201}$Tl uptake demonstrated on early images, or $T_{le}$, is believed to depend on blood–brain barrier dysfunction and increased regional blood flow, whereas the $^{201}$Tl uptake demonstrated on delayed images, or $T_{lo}$, may depend on active transport by the membrane pump of the tumor cells.$^{17}$ The RI is the ratio of the $T_{le}$ to the $T_{lo}$, which may be useful to distinguish between malignant and benign tumors.$^{5,8,14}$ During the present study we performed $^{201}$Tl SPECT studies in patients with hemangioblastomas and gliomas in the posterior fossa to compare $T_{le}$, $T_{lo}$, and RI values.

Clinical Material and Methods

Preoperative $^{201}$Tl SPECT studies were performed in nine patients who presented between April 1996 and December 2000 with posterior fossa hemangioblastomas (six primary and three recurrent lesions), five patients (six lesions) with posterior fossa gliomas (three anaplastic astrocytomas, one choroid plexus papilloma, and two pilocytic astrocytomas), and one patient with an adenocarcinoma that had metastasized to the brain (Table 1).

Brain images were obtained (Siemens MULTI SPECT scanner; Siemens Gammasonics, Hoffman Estates, IL) at 15 minutes (early image) and 3 hours (delayed image) after injection of thallium-201 (3 mCi) by using a $64 \times 64$ matrix with a Butterworth filter. Images were constructed in the transverse plane to facilitate comparison with MR
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**Indices and Statistical Analysis**

The $^{201}$Tl index ($T_{II}$ and $T_{ID}$) was defined as the ratio of the mean counts of tracer per pixel in the tumor to the mean counts of tracer per pixel in the contralateral homologous region. The lesion was located at the midline in three patients and thus the homologous region in the frontal lobe was used as the healthy region. The RI was calculated as ($T_{II}$/$T_{ID}$). Data were analyzed by using an unpaired Student t-test. A probability value less than 0.05 was considered significant.

**Results**

Table 1 shows the measured values in all patients. The $T_{II}$ ranged from 1.9 to 3.8 (mean ± SD 2.7 ± 0.7) in hemangioblastomas and 1.1 to 5.7 (mean ± SD 2.9 ± 1.7) in gliomas, with no significant difference between these values. The $T_{II}$ of the metastatic brain tumor was 5.6. The $T_{ID}$ ranged from 1 to 2.1 (mean ± SD 1.5 ± 0.4) in hemangioblastomas and 1 to 4.6 (mean ± SD 2.4 ± 1.6) in gliomas. The $T_{ID}$ tended to be lower in hemangioblastomas than in gliomas, but the difference was not statistically significant (p = 0.066). The $T_{II}$ of the metastatic brain tumor was 4. The RI ranged from 0.32 to 0.53 (mean ± SD 0.43 ± 0.07) in hemangioblastomas and 0 to 0.28 (mean ± SD 0.15 ± 0.1) in gliomas. The RI was significantly higher in hemangioblastomas than in gliomas (p < 0.01). The RI of the metastatic brain tumor was 0.29.

**Illustrative Cases**

**Case 1**

This 37-year-old man presented with a 2-month history of headaches. Magnetic resonance images revealed a 3-cm-wide cystic lesion in the left cerebellar hemisphere with thick wall enhancement (Fig. 1, upper). Angiograms confirmed the presence of a hypervascular mass lesion with retention of contrast agent into the venous phase. A $^{201}$Tl SPECT study demonstrated two different patterns of isotope uptake. During the early phase there was a moderately high uptake, with a $T_{II}$ of 2.3 (Fig. 1, lower). Thallium-201 was readily washed out from the lesion and during the delayed phase almost no retention could be observed, with a $T_{II}$ of 1.1 (Fig. 1, lower). The tumor was totally resected, and the histological diagnosis in this case was hemangioblastoma.

**Case 6**

This 53-year-old man presented with a 1-month history of headaches, nausea, and truncal ataxia. Magnetic resonance images revealed a 4.5-cm-wide solid enhanced mass with multiple cysts in the right cerebellar hemisphere (Fig. 2, upper). A $^{201}$Tl SPECT study revealed a moderately high uptake of tracer during the early phase, with a $T_{II}$ of 2.3, but almost no retention during the delayed phase, with a $T_{II}$ of 1.3 (Fig. 2, lower). In this case the tumor was totally resected, and the histological diagnosis was hemangioblastoma.

**Case 10**

This 58-year-old man presented with a 2-week history of headaches, vomiting, and truncal ataxia. The MR images revealed a 2-cm-wide diffuse solid enhanced mass in the right cerebellar hemisphere (Fig. 3, upper). A $^{201}$Tl SPECT study revealed a high uptake of isotope during the early phase, with a $T_{II}$ of 5.7, and a high retention during the delayed phase, with a $T_{II}$ of 4.6 (Fig. 3, lower). The tumor was totally resected, and the histological diagnosis in this case was anaplastic astrocytoma. The patient underwent hyperfractionated radiotherapy (72 Gy) and systemic injection of 1-(4-amino-2-methyl-5-pyrimidinyl)-methyl-3-(2-chloroethyl)-3-nitrosourea (ACNU).
Discussion

Findings of the present study demonstrate the diagnostic potential of $^{201}$Tl uptake for identifying hemangioblastomas. The $^{201}$Tl index of hemangioblastomas demonstrated moderately high uptake during the early phase, but almost no retention during the delayed phase. The $K^+$ analog $^{201}$Tl is directly taken up into malignant tumor cells by the $Na^+-K^+$ ATPase pump. Both biologically malignant and benign tumors, such as meningiomas, display high uptake of thallium-201.15 The $^{201}$Tl uptake observed on early images is believed to depend on blood–brain barrier dysfunction and increased regional blood flow.17 Hemangioblastomas are characterized histologically by two different cellular components; large vacuolated stromal cells and the reactive growth of endothelial cells. The reactive endothelial cells form a rich capillary network that provides a hypervascular tumor bed. This hypervascular tumor bed reflects the regional blood flow and increases the $^{201}$Tl index during the early phase in hemangioblastomas.

The $^{201}$Tl uptake observed on delayed images may depend on active transport by the membrane $Na^+-K^+$ ATPase pump of the tumor cells.12,17 Thallium has an affinity approximately 10 times greater than that of $K^+$ for the $K^+$-activating site of $Na^+-K^+$ ATPase and, once inside the cell, thallium is less readily released than $K^+$.4 Our finding of almost no $^{201}$Tl retention during the delayed phase supports the hypothesis that $Na^+-K^+$ ATPase activity is not increased in hemangioblastomas, compared with healthy brain parenchyma. The stromal cells probably represent

Fig. 1. Case 1. Representative neuroimaging findings of a cystic hemangioblastoma. Upper: Unenhanced (left) and gadolinium-enhanced (right) $T_1$-weighted MR images revealing a cystic lesion in the left cerebellar hemisphere with thick wall enhancement. Lower: Thallium-201 SPECT scans obtained during the early (left) and delayed (right) phases. The image obtained during the early phase reveals moderately high uptake of tracer, with a $T_I$ of 2.3, but the image obtained during the delayed phase demonstrates almost no retention, with a $T_D$ of 1.1.
the true neoplastic component of hemangioblastomas. The mitotic rate and the number of tumor cells entering the cell cycle are low in stromal cells, with a Ki-67 LI of less than 1%.3 The Na⁺-K⁺ ATPase activity does not directly reflect the tumor growth activity, as indicated by the Ki-67 LI. Nevertheless, the characteristics of stromal cells with a low Ki-67 LI may reflect the biologically benign neoplastic character of hemangioblastomas, assuming that membrane Na⁺-K⁺ ATPase pump activity is not increased.

The ²⁰¹Tl SPECT technique is useful for the evaluation of brain tumors and determination of the malignancy grade of glial tumors.⁵,⁶,¹⁴,¹⁵ The Tlₚ is significantly higher in high-grade gliomas (WHO Grades III and IV) than in low-grade gliomas (WHO Grades I and II),³ suggesting that the characteristics of thallium-201, which depend on the activity of membrane Na⁺-K⁺ ATPase, might be useful for the evaluation of both grade and malignancy of brain tumors. The difficulties encountered in arriving at the diagnosis of hemangioblastoma are related to the variations in the MR imaging appearance, which require exclusion of gliomas or metastatic brain tumors before a therapeutic strategy can be selected.

This study revealed that ²⁰¹Tl SPECT studies demonstrate moderately high isotope uptake during the early phase and no isotope retention during the delayed phase in hemangioblastomas. The corresponding values are variable in gliomas, ranging from no uptake to high uptake, and no statistical differences between gliomas and heman-
glioblastomas were found; however, the RI is significantly higher in hemangioblastomas than in gliomas. In the present study we included only one case of metastatic brain tumor; this lesion was found to have a low RI similar to that of gliomas. Previous studies have also demonstrated that the retention ratio of thallium-201 is significantly higher in metastatic brain tumors, such as high-grade astrocytomas, compared with the retention ratio of low-grade astrocytomas. The results of the present and previous studies indicate that 201 Tl SPECT studies provide additional information based on the RI for the differential diagnosis of hemangioblastoma.

Conclusions

Thallium-201 SPECT studies demonstrate high uptake of the tracer during the early phase and almost no retention during the delayed phase in hemangioblastomas. The results of the 201 Tl SPECT studies clearly reveal the biological characteristics of hemangioblastomas, that is, a regional high blood flow with a biologically benign nature. The results of the present study support the diagnostic value of 201 Tl SPECT studies to evaluate the grade and malignancy of brain tumors. This schema, although it is still incomplete, provides a framework for further mechanistic studies.

References

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