# Thallium-201 Retention in Focal Intracranial Lesions for Differential Diagnosis of Primary Lymphoma and Nonmalignant Lesions in AIDS Patients

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The purpose of this study was to determine whether $^{201}$Tl retention in focal intracranial lesions can help distinguish central nervous system (CNS) lymphoma from toxoplasmosis and other nonmalignant CNS lesions in patients with acquired immunodeficiency syndrome. **Methods:** Forty-nine patients who presented with focal lesions on CT and/or MRI had $^{201}$Tl brain SPECT studies (early and delayed image sets) performed shortly after admission. Early and delayed $^{201}$Tl uptake ratios were obtained for the positive studies, and the retention index of thallium was calculated (delayed/early target-to-background mean count ratio). **Results:** Twenty-nine patients had foci of significantly increased $^{201}$Tl uptake on the early images in regions of corresponding CT/MRI lesions. Ten of these patients had biopsy-proven lymphomas. Another patient was found to have metastatic adenocarcinoma. Twelve additional patients had a response to radiation therapy or a clinical course consistent with lymphoma and six patients had a false-positive SPECT study. The early uptake ratio could not separate malignant from nonmalignant lesions. The $^{201}$Tl retention index in patients with lymphomas (1.18 ± 0.16) was significantly higher than the retention index in adenocarcinoma (0.24) and in the six nonmalignant lesions (0.62 ± 0.07). The lowest retention index in patients with lymphoma was 1.07, and the highest retention index in nonmalignant lesions was 0.70. Twenty patients showed no $^{201}$Tl uptake in the regions of CT/MRI lesions. Three of them had biopsies consistent with a benign etiology, and one patient was diagnosed with tuberculosis. Fifteen patients improved clinically on antitoxoplasmosis medications alone, and one patient had CNS lymphoma. The overall sensitivity of $^{201}$Tl brain SPECT was 96%. The specificity was 76% by counting all studies with abnormal $^{201}$Tl uptake, but it increased to 100% when the retention index was also considered. **Conclusion:** The retention index increases the specificity of $^{201}$Tl brain SPECT in human immunodeficiency virus patients. In the presence of abnormal early $^{201}$Tl uptake, it is essential to perform delayed imaging and calculate the retention index to distinguish nonmalignant lesions from lymphoma. The absence of $^{201}$Tl uptake on early images at the site of a CT/MRI abnormality excludes the diagnosis of lymphoma with a high degree of confidence and delayed imaging is unnecessary.

**Key Words:** acquired immunodeficiency syndrome; central nervous system lymphoma; toxoplasmosis; thallium-201; retention index

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We have recently reported in a small series of patients that $^{201}$Tl SPECT can dramatically reduce the time to referral for a brain biopsy in patients with acquired immunodeficiency syndrome (AIDS), from a 1- to 2-wk interval to less than 72 hr (*1*). The main differential diagnosis of a cerebral focal mass lesion in human immunodeficiency virus (HIV) patients is between malignant lesions [central nervous system (CNS) lymphoma in 30% of focal lesions] and nonmalignant lesions (toxoplasmosis in 50% and progressive multifocal leukoencephalopathy in 10%–20% of patients, respectively) (*2*).

CNS lymphoma and nonmalignant mass lesions may present clinically and neuroradiologically in a similar manner (*2,3*). Although SPECT imaging with $^{201}$Tl has been shown to localize in brain tumors with a good target-to-background ratio (*4–6*), potential false-positive results in cases of nonmalignant lesions may occur (*7–9*). Quantitative methods aimed at increasing the specificity of thallium uptake in mass intracranial lesions were reported to distinguish high-grade from low-grade tumors or fibrosis and also were used to follow the effect of therapy (*5,6,10,11*).

Our previous study suggested that the retention index of $^{201}$Tl may be useful in patients with AIDS and abnormal intracranial $^{201}$Tl uptake. The purpose of this study was to prospectively apply the retention index of $^{201}$Tl in a larger patient population and determine whether the degree of retention in focal intracranial lesions can distinguish CNS lymphoma from toxoplasmosis and other nonmalignant CNS lesions.

## MATERIALS AND METHODS

We studied 49 patients (19 women, 30 men; age range 26–53 yr; mean age 39 yr) requiring differential diagnosis between cerebral toxoplasmosis and primary CNS lymphoma. All patients had focal intracranial mass lesions seen on CT and/or MRI. Clinical presentation varied from nonfocal symptoms of confusion and agitation to focal seizures, hemiparesis and hemiplegia. The serum of all patients was tested for antitoxoplasmosis IgG antibodies and reported as either positive or negative.

The final diagnosis was based on either biopsy or clinical improvement after specific therapy. All patients were under steroid therapy at the time of their thallium scans (ranging from 2 to 6 days).

Brain SPECT was performed 10 min after injecting 4 mCi (148 MBq) $^{201}$Tl intravenously. In 23 patients, delayed $^{201}$Tl SPECT was also performed at 3 hr postinjection. Scans were acquired on a triple-head gamma camera (Prism 3000; Picker International, Cleveland, OH) equipped with low-energy, high-resolution collimators. Projection data were acquired in a 64 × 64 matrix (pixel width of 4.45 mm) for 90 sec per projection sampling every 5.45°. A 40% window was centered over 74 keV and summed to a 20% window over 167 keV. Transverse, sagittal and coronal slices were reconstructed using a Butterworth prefilter (cutoff frequency = 0.25 cycles/cm; power factor = 5) with a ramp postfilter. No attenuation correction was applied.

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**TABLE 1**
Diagnostic Accuracy of Thallium-201 SPECT for Intracranial Lesions in AIDS Patients

| $^{201}$Tl | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| EU‡ | 96% | 76% | 79% | 95% |
| RI§ | 96% | 100% | 100% | 95% |

PPV = positive predictive value; NPV = negative predictive value; EU = early uptake ratio; RI = retention index.

The SPECT studies were examined using the CT/MRI images for anatomic correlation. A study was interpreted as consistent with a viable tumor if the uptake in the region of CT/MRI abnormality was clearly greater than the uptake in the corresponding region of the unaffected hemisphere.

For quantitative analysis, the transaxial image in which the lesion showed the greatest activity was selected, and a region of interest (ROI) was drawn around the lesion. A similar ROI was drawn in the contralateral brain. The average number of counts/pixel was determined for each ROI. The ratio of the average number of counts/pixel in the lesion to average number of counts/pixel in the normal brain (uptake ratio) was obtained for all patients with positive studies. In the 23 patients who had a delayed $^{201}$Tl SPECT, a retention index was calculated as delayed uptake ratio over early uptake ratio.

For statistical analysis, a two-tailed Student's t-test was used.

## RESULTS

Most patients had 1–10 ring-enhancing lesions on CT/MRI with brain edema and sometimes mass effect, but some lesions showed dense-homogeneous or irregular enhancement. Lesion size ranged from 2 mm to 5 cm (mean 2 cm).

Twenty-nine patients had foci of significantly increased $^{201}$Tl uptake in the regions of corresponding CT/MRI lesions. Ten of these patients had biopsy-proven diffuse large-cell lymphoma. Another patient was found to have metastatic adenocarcinoma. Nine patients had radiation therapy, without a biopsy, based on thallium results and CT/MRI appearance and improved clinically. Three patients did not respond to antitoxoplasmosis medications and died shortly after diagnosis. Six patients improved on antitoxoplasmosis medications and steroids alone, and they remained neurologically stable at 6 mo. These patients were considered false-positive cases. Four patients with lymphoma and the patient with adenocarcinoma had positive antitoxoplasmosis antibodies.

Twenty patients showed no thallium uptake in the coregion's CT abnormalities. Three of them had biopsies that showed toxoplasmosis, cerebral gliosis and a large-cell lymphoma, respectively. Fifteen other patients improved clinically on antitoxoplasmosis medications alone. One had cryptococcal meningitis and another patient was diagnosed with tuberculosis. The sensitivity of the thallium studies was 96% (23/24) and specificity without quantification was 76% (19/25) (Table 1).

The quantitative analysis (Fig. 1) showed the mean early uptake ratio in patients with lymphoma was 2.98 ± 1.95 and in patients with false-positive studies was 2.55 ± 0.97 (nonsignificant statistically). The mean retention index for lymphomas was 1.18 ± 0.16 (range 1.07–1.52). Figure 2 is of a 33-yr-old man with a ring-enhancing lymphoma in the right parietal lobe. The patient with adenocarcinoma had a retention index of 0.24, and the patients with false-positive thallium uptake had a mean retention index of 0.62 ± 0.07 (Fig. 3), both significantly lower than lymphoma ($p < 0.001$). The lowest retention index in patients with lymphoma was 1.07, and the highest retention

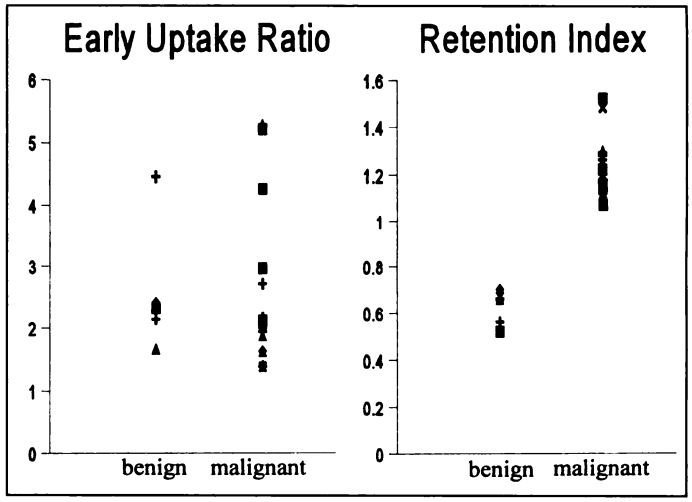


**FIGURE 1.** Distribution of $^{201}$Tl ratios in patients with central nervous system lymphoma and in patients with nonmalignant lesions.

index in nonmalignant lesions was 0.70. By using quantitative analysis, the specificity and the positive predictive value of the thallium studies increased from 76% and 79%, respectively, to 100%.

## DISCUSSION

The prevalence of HIV infection continues to rise. It is estimated that 650,000–900,000 individuals in the U.S. were infected with HIV by the end of 1992 (*12*). HIV is a lymphotrophic, as well as neurotrophic virus (*13*), and CNS involvement as the presenting complaint is seen in approximately 10% of patients. However, nearly 40% of patients eventually develop clinical signs and symptoms referable to the CNS (*14*). Neurologic symptoms are frequently headache, dementia, confusion and decreased memory, although symptoms suggestive of a mass lesion may also be present. The most common neurologic syndrome in the AIDS population is subacute encephalitis (*15,16*). This may affect 22%–36% of all patients with neurological symptoms. Imaging studies in this syndrome may be normal or may show mild cortical atrophy.

Infectious agents affecting the CNS are the next most frequent source of neurologically related complaints. The inappropriate immune response of the AIDS-infected host predisposes these patients to opportunistic infections. Various types of organisms may affect the CNS. Toxoplasmosis is the most frequent opportunistic infection to cause focal intracerebral lesions (50% of patients with neurologic problems). Other infectious processes include cytomegalic inclusion virus, herpes simplex virus, *Cryptococcus neoformans*, *Coccidioides immitis*, *Aspergillus fumigatus*, *Treponema pallidum*, mycobacteria, *Mucor* species, *Candida albicans* and, rarely, bacteria (*15,17,18*). Primary CNS lymphoma is the next most common cause of focal intracranial lesions, and 1.9% of AIDS patients develop primary CNS lymphoma (*2,19,20*).

Clinical findings and laboratory studies are not helpful in separating these entities. There are no differentiating features on CT or MRI to distinguish patients with toxoplasmosis from those with lymphoma (*21*). Both processes often appear as ring-enhancing lesions on CT and MRI with mild to moderate edema and mass effect (*2,3*). CNS lymphoma and toxoplasmosis can present as singular or multiple lesions and may occur anywhere in the brain. In several patients with normal CT, the autopsy revealed CNS disease (*21*). MRI is more sensitive than CT, locating a higher proportion of the lesions ultimately found at biopsy (*2*). In one study (*3*), two of four AIDS patients

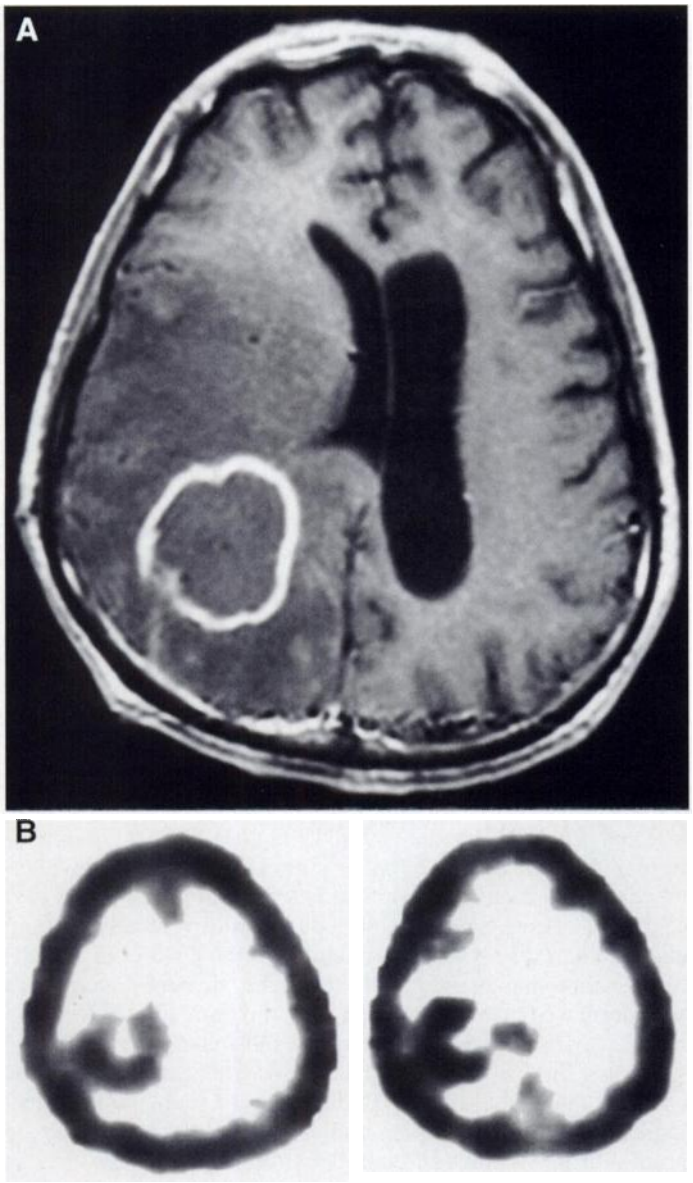


**FIGURE 2.** A 33-yr-old man with human immunodeficiency virus who presented with seizures. (A) Contrast-enhanced MR scan shows large ring-enhancing lesion in right parietal lobe. There is significant surrounding edema and mass effect. (B) Thallium-201 SPECT shows annular-shaped uptake in same region on early images (left) with significant retention on delayed images (right). Biopsy showed large-cell lymphoma.

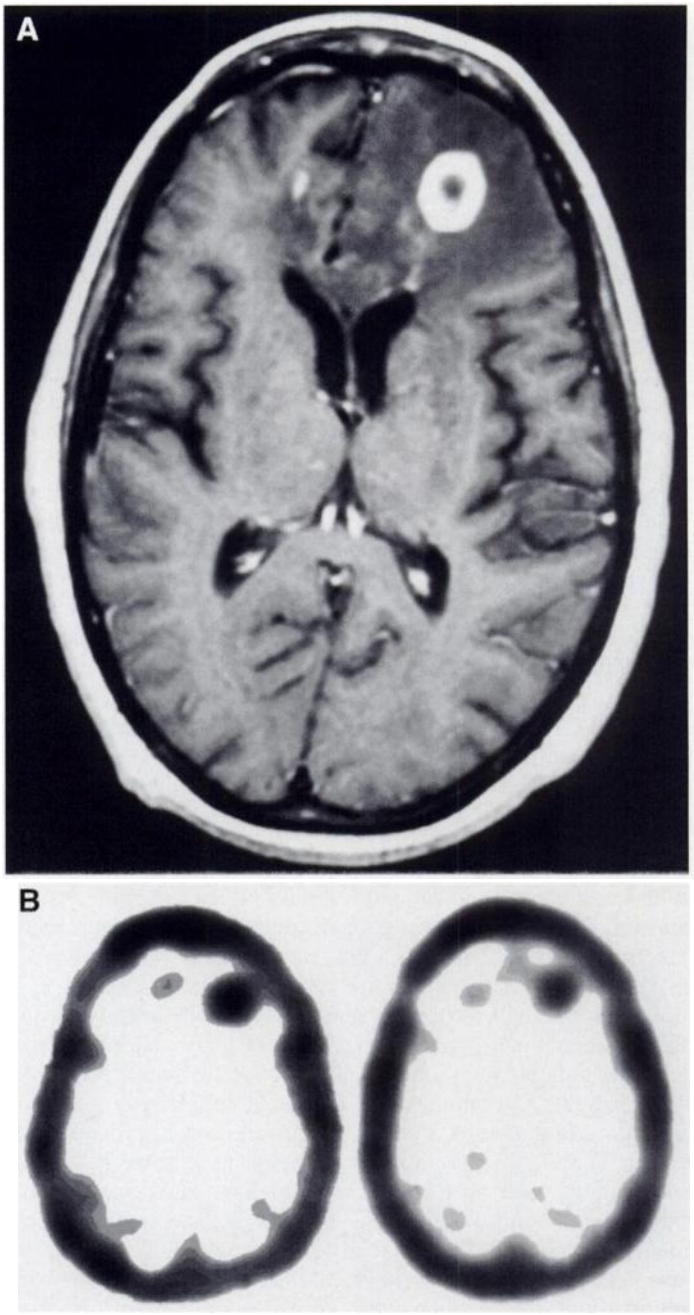


**FIGURE 3.** A 35-yr-old man with human immunodeficiency virus who presented with seizures. (A) Contrast-enhanced MR scan shows thick-walled ring-enhancing lesion in left frontal lobe with surrounding edema. (B) Thallium-201 SPECT shows prominent focus of activity in left frontal lobe on early images (left) with less avid uptake on delayed images (right, retention index = 0.67).

demonstrated entirely normal MRI despite autopsy demonstration of widespread malignant lymphoma in one and multifocal lymphoma in the other. AIDS-related lymphomas usually look like rings or targets on MR images (*22*). However, toxoplasmosis abscesses appear also as focal mass lesions with ring enhancement.

Assuming that a CNS mass lesion is more likely due to toxoplasmosis, most clinicians initially administer pyrimethamine and sulfadiazine for a presumptive diagnosis of toxoplasmosis whenever radiographic studies reveal intracranial mass lesions. Treatment of toxoplasmosis is frequently limited by adverse drug effects. Reported rates of toxicity range from 38% to 71% (*23*). The inability to diagnose lymphoma radiographically before the empirical antibiotic trial has delayed effective treatment for patients with lymphoma. During antitoxoplasmosis therapy, tumor progression was reported in 13 of 17 patients with AIDS-related lymphoma and new lesions developed in 3 patients (*24*). In addition, it is essential to initiate radiation therapy early for optimal effectiveness (*25,26*). Primary CNS lymphoma responds favorably to radiation therapy, although significant long-term effects on patient survival have not been demonstrated (*27*).

First used as a heart imaging agent, $^{201}$Tl was used subsequently as a tumor imaging agent, including primary and metastatic brain lesions (*28,29*). Thallium-201 SPECT imaging has been used both to diagnose the tumor grade preoperatively and to monitor patients after surgery and treatment with radiation and/or chemotherapy to determine tumor burden (*4*). The affinity of $^{201}$Tl for tumor tissue is not completely understood. The extraction of $^{201}$Tl is primarily mediated through the Na(+)-K+ ATPase pump system in tumor cells (*30*). Other contributing factors have been suggested (*30–33*).

Accumulation of $^{201}$Tl at the site of CT/MRI abnormality is highly suggestive of a viable tumor. Previous investigators have used the early target-to-background ratio and the retention of $^{201}$Tl to accurately identify viable intracranial tumors after chemotherapy and radiotherapy (*10,11*). The use of thallium indices was reported to increase the specificity of abnormal thallium activity by separating malignant lesions (high uptake) from low-grade tumors or postradiation changes (low uptake). It was evident that metabolically active tumor tissue would accumulate $^{201}$Tl to a much higher degree than nonviable necrotic tissue. Some investigators have shown a good correlation between retention index and tumor histology (*10*), whereas other investigators have been unable to distinguish between primary and metastatic tumors using $^{201}$Tl SPECT (*11*).

Nonetheless, increased thallium uptake was also reported in other nonmalignant lesions such as infarcts and postradiation changes (*7–9*). Isolated reports of increased thallium uptake in patients with infection have been reported in pulmonary actinomycosis, bacterial abscess and intracerebral candidiasis (*34,35*). We have noticed, in several patients, focal increased $^{201}$Tl accumulation in patients with CNS toxoplasmosis, which may erroneously suggest the diagnosis of a viable tumor. Although the early uptake was slightly lower in patients with nonmalignant lesions, the difference was not significant statistically. However, the use of the thallium retention index in the lesions increased the specificity of abnormal $^{201}$Tl uptake from 76% to 100% in our patient population. A cutoff value of 1.00 could discriminate lymphoma from toxoplasmosis in 100% of patients. It is conceivable that increased blood flow to the site of a toxoplasmosis abscess and the disruption of the blood-brain barrier may occasionally accentuate $^{201}$Tl uptake in nonmalignant inflammatory lesions.

## CONCLUSION

We found, in a large cohort of patients with AIDS, that $^{201}$Tl SPECT is highly sensitive for the differential diagnosis of focal brain lesions. The absence of $^{201}$Tl uptake on early images at the site of a CT/MRI abnormality excludes the diagnosis of lymphoma with a high degree of confidence. The specificity of the study is greatly enhanced when using the retention index of $^{201}$Tl. A ratio $> 1.00$ can distinguish lymphoma from nonmalignant lesions.


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## REFERENCES


1. Lorberboym M, Estok L, Machac J, et al. Rapid differential diagnosis of cerebral toxoplasmosis and primary CNS lymphoma by $^{201}$Tl SPECT. *J Nucl Med* 1996;37:1150–1154.
2. Ciricillo SF, Rosenblum ML. Use of CT and MR to distinguish intracranial lesions and to define the need for biopsy in AIDS patients. *J Neurosurg* 1990;73:720–724.
3. Kupfer MC, Zee CS, Colletti PM, Boswell WD, Rhodes RTI. MRI evaluation of AIDS-related encephalopathy: toxoplasmosis vs. lymphoma. *Magn Reson Imaging* 1990;8:51–57.
4. Black KL, Hawkins RA, Kim KT, et al. Use of $^{201}$Tl SPECT to quantitate malignancy grade of gliomas. *J Neurosurg* 1989;71:342–346.
5. Lorberboym M, Mandell LR, Mosesson R, et al. The role of $^{201}$Tl uptake and retention in intracranial tumors after radiotherapy. *J Nucl Med* 1997;38:223–226.
6. Lorberboym M, Baram J, Feibel M, Hercbergs A, Lieberman L. A prospective evaluation of $^{201}$Tl single photon emission computerized tomography for brain tumor burden. *Int J Radiat Oncol Biol Phys* 1995;32:249–254.
7. Krishna L, Slizofski WJ, Katsetos CD, et al. Abnormal intracerebral thallium localization in a bacterial brain abscess. *J Nucl Med* 1992;33:2017.
8. Moody EB, Hodes JE, Walsh JW, Thornsberry S. Thallium-avid cerebral radiation necrosis. *Clin Nucl Med* 1995;20:389–390.
9. Bernat I, Toth G, Kovacs L. Tumour-like $^{201}$Tl accumulation in brain infarcts, an unexpected finding on single-photon emission tomography. *Eur J Nucl Med* 1994;21:189.
10. Moustafa HM, Omar WM, Ezzat I, Ziada GA, el-Ghonimy EG. Thallium-201 single photon emission tomography in the evaluation of residual and recurrent astrocytoma. *Nucl Med Commun* 1994;15:140–143.
11. Yoshii Y, Satou M, Yamamoto T, et al. Experimental evaluation of the usefulness of $^{201}$Tl single photon emission tomography in the investigation and characterization of brain tumours in man and their response to treatment. *Eur J Nucl Med* 1993;20:39–45.
12. Karon JM, Rosenberg PS, McQuillan G, et al. Prevalence of HIV infection in the United States, 1984–1992. *JAMA* 1996;276:126–131.
13. Shaw GM, Harper ME, Hahn BH, et al. HTLV-III infection in brains of children and adults with AIDS encephalopathy. *Science* 1985;227:177–182.
14. Levy RM, Pons VG, Rosenblum ML. Central nervous system mass lesions in the acquired immunodeficiency syndrome (AIDS). *J Neurosurg* 1984;61:9–16.
15. Levy RM, Bredesen DE, Rosenblum ML. Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): experience at UCSF and review of the literature. *J Neurosurg* 1985;62:475–495.
16. Nielsen SL, Petito CK, Urmacher CD, Posner JB. Subacute encephalitis in acquired immune deficiency syndrome: a postmortem study. *Am J Clin Pathol* 1984;82:678–682.
17. Sze G, Brant Zawadzki MN, Norman D, Newton TH. The neuroradiology of AIDS. *Semin Roentgenol* 1987;22:42–53.
18. Whelan MA, Kricheff II, Handler M, et al. Acquired immunodeficiency syndrome: cerebral computed tomographic manifestations. *Radiology* 1983;149:477–484.
19. Levy RM, Bredesen DE. Central nervous system syndromes associated with AIDS. In: Rosenblum ML, Levy RM, Bredesen DE, eds. AIDS and the nervous system. New York: Raven, 1987.
20. Luft BJ, Remington JS. AIDS commentary. Toxoplasmic encephalitis. *J Infect Dis* 1988;157:1–6.
21. Levy RM, Rosenbloom S, Perrett LV. Neuroradiologic findings in AIDS: a review of 200 cases. *AJR* 1986;147:977–983.
22. Schwaighofer BW, Hesselink JR, Press GA, Wolf RL, Healy ME, Berthoty DP. Primary intracranial CNS lymphoma: MR manifestations. *AJNR* 1989;10:725–729.
23. Porter SB, Sande MA. Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. *N Engl J Med* 1992;327:1643–1648.
24. Goldstein JD, Zeifer B, Chao C, et al. CT appearance of primary CNS lymphoma in patients with acquired immunodeficiency syndrome. *J Comput Assist Tomogr* 1991;15:39–44.
25. Baumgartner JE, Rachlin JR, Beckstead JH, et al. Primary central nervous system lymphomas: natural history and response to radiation therapy in 55 patients with acquired immunodeficiency syndrome. *J Neurosurg* 1990;73:206–211.
26. Formenti SC, Gill PS, Lean E, et al. Primary central nervous system lymphoma in AIDS. Results of radiation therapy. *Cancer* 1989;63:1101–1107.
27. Rosenblum ML, Levy RM, Bredesen DE, So YT, Wara W, Ziegler JL. Primary central nervous system lymphomas in patients with AIDS. *Ann Neurol* 1988;23(suppl):S13–S16.
28. Ancri D, Basset JY, Lonchampt MF, Etavard C. Diagnosis of cerebral lesions by thallium 201. *Radiology* 1978;128:417–422.
29. Ancri D, Basset JY. Diagnosis of cerebral metastasis by $^{201}$Tl. *Br J Radiol* 1980;53:443–453.
30. Chin BB, Zukerberg BW, Buchpiguel C, Alavi A. Thallium-201 uptake in lung cancer. *J Nucl Med* 1995;36:1514–1519.
31. Sessler MJ, Geck P, Maul FD, et al. New aspects of cellular thallium uptake: $Tl^+$-$Na^+$-$^2Cl$-cotransport is the central mechanism of ion uptake. *Nuklearmedizin* 1986;23:24–27.
32. Winchell HS. Mechanisms for localization of radiopharmaceuticals in neoplasms. *Semin Nucl Med* 1976;6:371–378.
33. Brismar T, Collins VP, Kesselberg M. Thallium-201 uptake relates to membrane potential and potassium permeability in human glioma cells. *Brain Res* 1989;500:30–36.
34. Aktolun C, Demirel D, Kir M, Bayhan H, Maden HA. Technetium-99m-MIBI and $^{201}$Tl uptake in pulmonary actinomycosis. *J Nucl Med* 1991;32:1429–1431.
35. Tonami N, Matsuda H, Ooba H, et al. Thallium-201 accumulation in cerebral candidiasis: unexpected finding on SPECT. *Clin Nucl Med* 1990;15:397–400.