

# Analysis of the utility of diffusion-weighted MRI and apparent diffusion coefficient values in distinguishing central nervous system toxoplasmosis from lymphoma

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## Abstract

**Introduction** Toxoplasmosis and lymphoma are common lesions of the central nervous system in patients with AIDS. It is often difficult to distinguish between these lesions both clinically and radiographically. Previous research has demonstrated restricted diffusion within cerebral lymphomas and bacterial abscesses. However, little work has been done to evaluate the diffusion characteristics of toxoplasmosis lesions. This study was designed to explore further the utility of diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps and values in making the distinction between toxoplasmosis and lymphoma.

**Methods** The magnetic resonance imaging (MRI) studies of 36 patients, including 22 with toxoplasmosis (all of whom had AIDS) and 14 with lymphoma (8 of whom had AIDS), at two institutions were reviewed retrospectively. The characteristics of the lesions on DWI were evaluated, and the ADC ratios of the lesions were calculated and compared.

**Results** There was significant overlap of the ADC ratios of toxoplasma and lymphoma, most notably in the intermediate (1.0–1.6) range. There was variability in ADC ratios even among different lesions in the same patient. In only a minority of the lymphoma patients were the ADC ratios low enough to suggest the correct diagnosis.

**Conclusion** Our study showed that toxoplasmosis exhibits a wide spectrum of diffusion characteristics with ADC ratios which have significant overlap with those of lymphoma. Therefore, in the majority of patients, ADC ratios are not definitive in making the distinction between toxoplasmosis and lymphoma.

**Keywords** Diffusion · Toxoplasmosis · Lymphoma

## Introduction

Toxoplasmosis and lymphoma are common lesions of the central nervous system in patients with AIDS. It is often difficult to distinguish between these lesions both clinically and radiographically, as both entities may present as enhancing lesions on computed tomography (CT) and magnetic resonance imaging (MRI) examinations of the brain [1]. Because the treatment of these lesions differs significantly, it is an important distinction to make, as the implementation of incorrect therapeutic measures and/or a delay in appropriate therapy may result in substantial patient morbidity and mortality. The use of thallium-201 brain SPECT in AIDS patients has been proven to be very helpful, but the published accuracy is 57%, the positive predictive value 43%, and the negative predictive value 71% [2, 3]. The MR spectroscopic pattern of toxoplasmosis lesions is nonspecific and shows significant overlap with spectra found in lymphoma [4]. The potential use of F-18 fluorodeoxyglucose (FDG)-positron emission tomography (PET) in differentiating lymphoma from toxoplasmosis in AIDS patients has been also examined in a limited number of patients [5].

Previous research has demonstrated restricted diffusion within lymphomatous lesions and bacterial abscesses in the brain [6]. However, little work has been done to evaluate

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**Table 1** Distribution of ADC ratios

ADC ratio	No. of toxoplasmosis lesions	No. of lymphoma lesions
<1.0	1	10
1.0–1.6	24	13
>1.6	18	6

the diffusion characteristics of toxoplasmosis lesions. In a study of 21 patients performed by Camacho et al. in 2003 [7], the ADC ratios of 13 toxoplasmosis and 8 lymphoma lesions were calculated. None of the toxoplasmosis lesions was found to have an ADC ratio less than 1.0, and none of the lymphoma lesions was found to have an ADC ratio greater than 1.6. These results suggest that ADC ratios may be helpful in making the distinction. However, work at our institutions has revealed that there may be a wider and less characteristic spectrum of ADC values in toxoplasmosis lesions than previously thought.

We hypothesized that DWI and ADC values used without other methods are not reliable in the distinction between toxoplasmosis and lymphoma.

## Methods

The MRI studies of 36 patients, including 22 with CNS toxoplasmosis (all of whom had AIDS) and 14 with lymphoma (8 of whom had AIDS), at two institutions were reviewed retrospectively. In these patients, the diagnosis of toxoplasmosis was made based on a favorable response to medical therapy for toxoplasmosis, as evidenced by improvement in clinical symptoms and radiologic findings after treatment. None of the patients had been treated at the time the studies were performed. Although all patients in our sample were treated, only their initial (pretreatment) MR examinations were utilized for data collection. The diagnosis of lymphoma was made by positive thallium-201 SPECT in 7 of the 14 lymphoma patients and was biopsy-proven in six, and autopsy proven in one.

All studies were performed on 1.5-T clinical systems. The following sequences were performed in all patients: 2 mm coronal T2-W imaging, axial FLAIR, and axial, coronal and sagittal T1-W imaging before and after

**Table 2** Comparison of data sets – toxoplasma vs. lymphoma

	Toxoplasma	Lymphoma
No. of patients	22	14
No. of lesions	43	29
ADC ratios		
Range	0.8–2.8	0.2–2.5
Median	1.6	1.2

**Table 3** Comparison of data sets – lymphoma patients with and without AIDS

	With AIDS	Without AIDS
No. of patients	8	6
No. of lesions	16	13
ADC ratios		
Range	0.2–2.5	0.7–2.0
Median	1.3	1.0

gadolinium injection. A single-shot, multisection, spin-echo, echo-planar pulse sequence (4116/89) was used for DWI. We collected the DWI in three directions (X, Y, Z) with b values of 0, 500 and 1,000 s/mm<sup>2</sup>, a field-of-view of 230 mm, and a matrix of 128×128 or 256×256, with an acquisition time of 34 s.

Signal intensities on DW images and ADC maps were evaluated. The ADC ratios of the lesions were calculated. For the purposes of this study, the ADC ratio was defined as the ratio of an ADC value of a region of interest (ROI) within the lesion to the ADC value of an ROI in the contralateral normal white matter. The ROI utilized for ADC ratio calculation was circular, and it was placed in the center of the lesion. The diameter of the ROI was half of the total diameter of the lesion. Only lesions with an enhancing component measuring 1 cm or greater were included. This method of calculating the ADC ratio was identical to that employed by Camacho et al. [7] so that an appropriate comparison could be made between the two studies.

For statistical analysis two tests were performed: an unpaired Student's *t*-test and the Mann-Whitney test.

This study was approved by the institutional review board of the affiliated university (protocol no. 2004/022B).

## Results

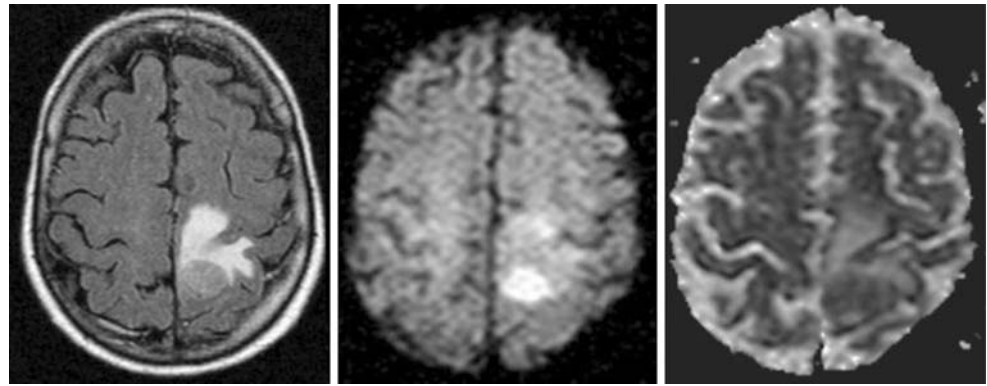
### Conventional sequences

The T2 signal, morphology, and enhancement characteristics of both the toxoplasmosis and lymphoma lesions were highly variable. On T2-WI, some were hyperintense, while others were isointense to normal brain parenchyma. Others were heterogeneous, containing areas of mixed high,

**Table 4** Distribution of ADC ratios (by percentage)

ADC ratio	Toxoplasmosis lesions (%)	Lymphoma lesions (%)
<1.0	2	34
1.0–1.6	56	45
>1.6	42	21

**Fig. 1** Left parietal lymphoma with restricted diffusion (ADC ratio 0.7). FLAIR image (*left*) demonstrates an isointense lesion with high-signal edema anteriorly. The lesion itself is hyperintense on DWI (*center*) and hypointense on the ADC map (*right*), consistent with restricted diffusion

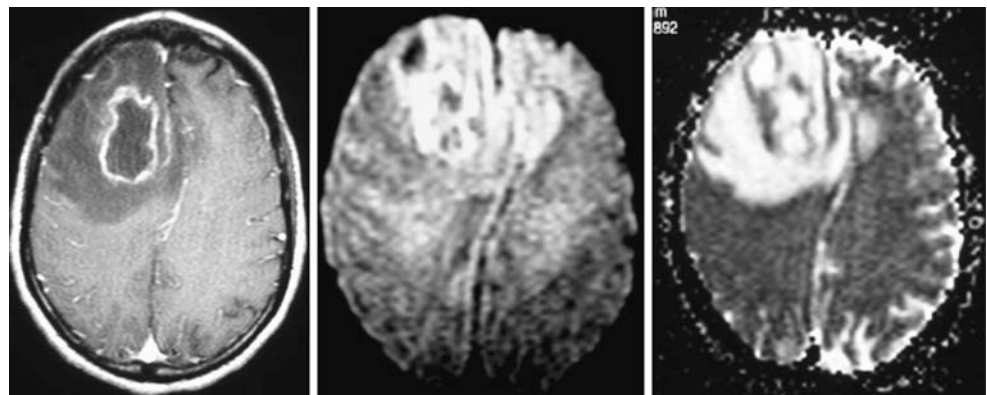


isointense, and low T2 signal. Some lesions demonstrated a ring pattern or heterogeneous enhancement, while others were solid and more homogeneous.

#### Diffusion-weighted MR imaging and ADC measurements

The ADC ratios measured are listed in Tables 1 and 2. Statistics for the lymphoma patients with and without AIDS are shown in Table 3. Table 4 shows the distribution of ADC ratios by percentage. There was significant overlap of toxoplasmosis and lymphoma, most notably in the intermediate (1.0–1.6) range of ADC ratios. Multiple patterns of diffusion were observed (visually) in both types of lesions, including restricted diffusion (Fig. 1), increased diffusibility (Figs. 2 and 3), normal diffusion, T2 “shine-through”, cerebrospinal fluid (CSF) equivalence, and mixed and indeterminate patterns (Figs. 4 and 5b). There was variability of ADC ratios, even between different lesions within the same patient (Fig. 5). Of the 11 patients with toxoplasmosis lesions with ADC ratios greater than 1.6, three also had lesions in the intermediate (1.0–1.6) category. Of the six patients with lymphoma lesions with ADC ratios greater than 1.6, five also had lesions in the intermediate category. No statistically significant difference was observed using the Mann-Whitney test comparing the three groups ( $P=0.7$ ).

**Fig. 2** Increased diffusibility in a patient with lymphoma (ADC ratio 2.5). The T1-W image after gadolinium administration (*left*) shows a ring-enhancing lesion in the right frontal lobe. DWI (*center*) demonstrates foci of low signal within the center of the lesion with high signal at the corresponding location on the ADC map (*right*), consistent with increased diffusibility. An ADC ratio of 2.5 was calculated for this lesion

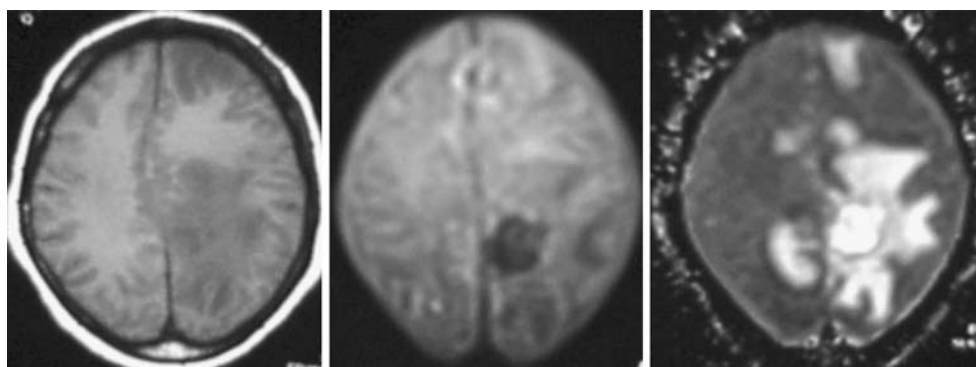


#### Discussion

Based on imaging findings on conventional MR sequences, cerebral toxoplasmosis cannot be distinguished from primary cerebral lymphoma. Early reports of MR imaging findings in AIDS patients suggested lymphoma if the lesion was solitary, and toxoplasmosis in those with multiple lesions [8, 9]. Further studies have shown that the number of lesions, the signal intensities of the lesions, their location, and their appearance on postcontrast images, are not reliable factors in differentiation between those two entities. Signal intensity on T2-W MR images is also not helpful, as both entities may show low signal [10, 11]. Nonenhancing lymphomatous lesions have been also reported, as in one study where 15 lymphomatous lesions in four patients with AIDS showed no enhancement [12]. Approximately 3.4% of primary central nervous system lymphoma lesions will show no enhancement in immunocompetent patients, especially in those receiving steroids before imaging [13].

New MR methods have been introduced to improve differentiation, such as MR spectroscopy and MR perfusion imaging. The MR spectroscopic pattern of toxoplasmosis lesions is nonspecific, consistent with anaerobic inflammation within the abscess. In lymphoma, an increase of lactate and lipids, as well as an elevated choline peak, have been described. Chinn et al. have studied MR spectra from 18 toxoplasmosis and 9 lymphoma lesions [4]. Visual analysis

**Fig. 3** Increased diffusibility in a toxoplasmosis lesion. Axial T1-W image (*left*) shows a lesion in the left parietal lobe. DWI (*center*) demonstrates low signal at the corresponding location with increased signal on the ADC map (*right*). An ADC ratio of 2.8 was calculated for this lesion, indicating increased diffusibility



in their study failed to differentiate between toxoplasmosis and lymphoma. An important variable for MR spectra is the maturity of the lesions, as well as the presence of necrosis. Although much work has been done, MR spectroscopy cannot replace conventional MR imaging in differentiation of toxoplasmosis and lymphoma.

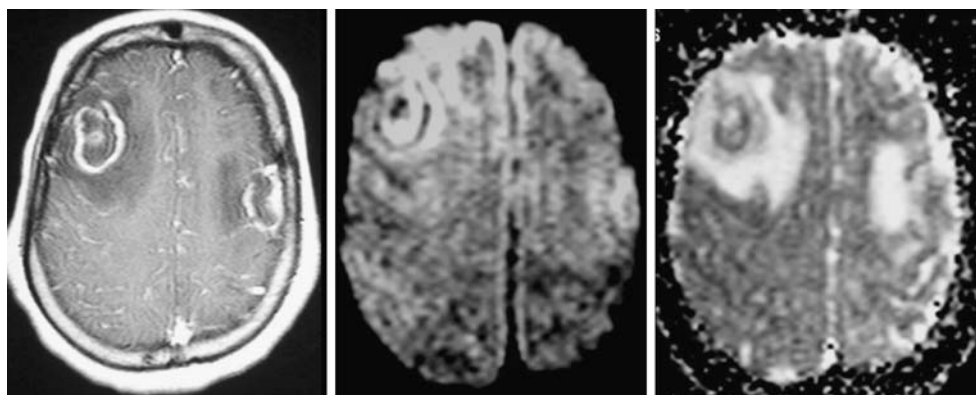
Prospective evaluation of 13 patients with focal brain lesions with perfusion MR imaging showed reduced regional cerebral blood volume (rCBV) in toxoplasmosis lesions, and increased rCBV in lymphoma [14]. Reduced rCBV in toxoplasmosis is probably due to a lack of vasculature within the abscess, while the hypervascularity of lymphoma is the reason for increased rCBV in lymphoma.

Diffusion is the random movement of water molecules as a result of their kinetic energy [15]. Diffusion-weighted MRI quantifies the diffusion of water molecules with a value known as the apparent diffusion coefficient. Diffusion is least restricted in free water, which does not contain protein or other molecules which interfere with the movement of the water molecules. Conversely, the diffusion of water is more restricted inside cells, which contain larger quantities of proteins and other molecules than the extracellular spaces of the body [15]. Consequently, highly cellular tumors, such as lymphoma, often exhibit restricted diffusion [16]. Similarly, in abscesses, which consist of cellular debris and inflammatory proteins, the diffusion of water molecules would also be expected to be restricted [6].

The most common presentation of a primary CNS lymphoma in an immunocompetent patient is an intensely enhancing mass which is homogeneous in signal and often isointense or hypointense to normal brain on T1-W and T2-W images [13]. In immunocompromised patients such as those with AIDS, lymphoma is often less cellular secondary to necrosis; large portions of the tumor may consist of fluid rather than cells [12, 13]. Necrotic lymphoma lesions in AIDS patients are less likely to show restricted diffusion owing to their relative hypocellularity. When a lymphoma lesion is necrotic, portions of the lesion which may remain highly cellular, such as the enhancing rim, may show restricted diffusion, while the necrotic portions of the lesion do not. Therefore, the ADC values of the lesion may vary depending upon where the measurement is taken. In this study, the ROI was placed in the center of the lesion, which was often necrotic. It is the suspicion of the authors that the placement of the ROI within the center of these lesions (often necrotic and fluid-filled) in both the toxoplasmosis and lymphoma lesions may partially explain the overlap of ADC measurements.

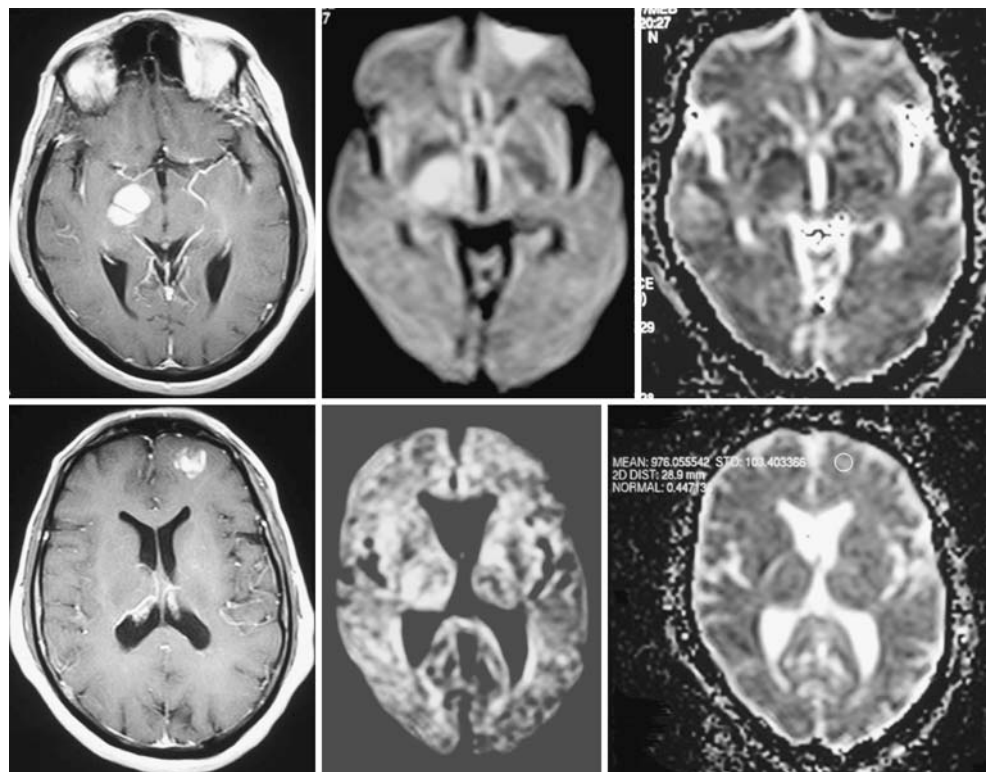
Although a protozoan rather than a bacterium, *Toxoplasma gondii* causes abscess formation in the brains of immunocompromised patients. Toxoplasmosis lesions have been shown to progress through various stages of histologic organization, including necrotizing encephalitis, coagulative necrosis, and organizing abscess with some lesions containing elements of all three [17]. These distinct

**Fig. 4** Toxoplasmosis lesions with intermediate ADC ratios of 1.3 and 1.1. T1-W image after gadolinium administration (*left*) shows ring-enhancing lesions in the bilateral frontal lobes. DWI (*center*) and ADC map (*right*) show heterogeneous signal in both lesions. The ADC ratio of the lesion in the right frontal lobe was 1.3, and the ADC ratio of the lesion in the left frontal lobe was 1.1





**Fig. 5** Restricted (**a** ADC ratio 0.78) and intermediate (**b** ADC ratio 1.3) lesions in the same patient with biopsy-proven lymphoma. **a** T1-W image (*left*) shows a solid enhancing lesion involving the right cerebral peduncle and surrounding area with visibly restricted diffusion (*center* high signal on DWI, *right* low signal on the ADC map). The ADC ratio for this lesion was 0.78. **b** The left frontal lesion in the same patient, which was biopsy-proven (*left* T1 after gadolinium administration), showed indeterminate/mixed signal on both DWI (*center*) and the ADC map (*right*). This lesion yielded an ADC ratio of 1.3, a value in the intermediate range



histologic stages may account for some of the variability of ADC values obtained within the toxoplasmosis lesions. The histologic composition of the lesion may be altered by treatment. Although none of the patients in our study had been treated at the time of their examination, in day-to-day practice, many patients examined by MRI will have been treated to some extent, which may complicate the findings on DWI and ADC maps and render them less useful.

In the study by Camacho et al. mentioned above, the investigators examined a series of 13 toxoplasmosis lesions in seven patients and eight lymphoma lesions in four patients [7]. They found mean ADC ratios of 1.63 for the toxoplasmosis lesions and 1.14 for lymphoma and that ADC ratios greater than 1.6 were associated only with toxoplasmosis. They therefore concluded that ADC ratios are helpful in making the distinction between toxoplasmosis and lymphoma. Nevertheless, the majority of their patients had overlapping ADC values, such that a definitive diagnosis could be made in only 9 of their 21 patients (43%). Although the results of our studies are similar in that

both demonstrate significant overlap, we feel that the use of ADC ratios may not be a practical means of making the distinction, because the majority of patients fall into the intermediate category. In other words, while the findings of the two studies are quite similar, our interpretation of the results is different. Our study included a larger sample size (72 lesions in 36 patients at two institutions). We found significant overlap of ADC ratios of toxoplasmosis lesions with those of lymphoma (in the range 0.8–2.5). Of the lymphoma lesions in our series, 21% had ADC ratios greater than 1.6. A correct diagnosis of lymphoma could have been made based on the ADC ratios in only 9 of our 29 lymphoma lesions (31%).

The limitations of this study include the following. In only 6 of the 14 lymphoma patients was the lymphoma biopsy-proven. However, none of the biopsy-proven lymphoma lesions had ADC ratios less than 1.0, indicating that even in pathologically proven lymphoma lesions, the ADC ratios remain in the nondiagnostic range. Furthermore, although eight lymphoma patients did not have biopsy-proven lymphoma, seven of these patients had positive thallium 201-SPECT scans. Positive thallium 201-SPECT was chosen as an inclusion criterion for the lymphoma patients, because it has become a widely accepted tool for making this diagnosis at our institutions and others. In one study thallium-201-SPECT was found to have 100% sensitivity and 93% specificity for the identification of CNS lymphoma [18], although in another 86% and 83% were found, respectively [19]. An additional limitation of

**Table 5** Lymphoma lesions in which ADC measurements were taken at two locations

Patient	ADC ratio in solid portion of lesion	ADC ratio in necrotic portion
1	1.1	2.5
2	1.8	1.6
3	1.0	1.9

the study was the placement of the ROI for ADC value calculation only within the center of the lesion, which may explain overlap between necrotic lymphoma lesions and toxoplasmosis abscesses. There were three patients with lymphoma lesions in whom we obtained measurements in both the center of the lesions and at the periphery (Table 5). Because none of the ADC ratios were below 1.0, placing the ROI at a different location within the lesion would not have helped to make the distinction between toxoplasmosis and lymphoma in these patients.

## Conclusion

Toxoplasmosis exhibits a wide spectrum of diffusion characteristics with ADC ratios ranging from 0.8 to 2.8, which have significant overlap with those of lymphoma. Therefore, in a majority of patients, ADC ratios are not definitive in making the distinction between toxoplasmosis and lymphoma. However, in the minority of patients with ADC ratios below 0.8, a diagnosis of lymphoma should be favored.

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**Conflict of interest statement** We declare that we have no conflict of interest.

## References

- Osborn AG, Blaser SI, Salzman KL (2004) Diagnostic imaging: brain. WB Saunders, Philadelphia, pp 122–123
- Ruiz A, Ganz WI, Post MJD et al (1994) Use of Thallium-201 Brain SPECT to differentiate cerebral lymphoma from toxoplasma encephalitis in AIDS patients. *AJNR Am J Neuroradiol* 15:1885–1894
- Licho R, Litofsky NS, Senitko M et al (2002) Inaccuracy of Tl-201 brain SPECT in distinguishing cerebral infections from lymphoma in patients with AIDS. *Clin Nucl Med* 27:81–86
- Chinn RJS, Wilkinson ID, Hall-Craggs MA et al (1995) Toxoplasmosis and primary central nervous system lymphoma in HIV infection: diagnosis with MR spectroscopy. *Radiology* 197:649–654
- Villringer K, Jager H, Dichgans M et al (1995) Differential diagnosis of CNS lesions in AIDS patients by FDG-PET. *J Comput Assist Tomogr* 19:532–536
- Desprechins B, Stadnik T, Koerts G, Shabana W, Breucq C, Osteaux M (1999) Use of diffusion-weighted MR imaging in differential diagnosis between intracerebral necrotic tumors and cerebral abscesses. *AJNR Am J Neuroradiol* 20:1252–1257
- Camacho DL, Smith JK, Castillo M (2003) Differentiation of toxoplasmosis and lymphoma in AIDS patients by using apparent diffusion coefficients. *AJNR Am J Neuroradiol* 24:633–637
- Dina TS (1991) Primary central nervous system lymphoma versus toxoplasmosis in AIDS. *Radiology* 179:823–828
- Kupfer MC, Zee CS, Colletti PM et al (1990) MRI evaluation of AIDS related encephalopathy: toxoplasmosis vs lymphomas. *Magn Reson Imaging* 8:51–57
- Rhoades RA, Tanner GA (1995) Medical physiology. Little, Brown, and Company, New York, pp 17–18
- Schwartz KM, Erickson BJ, Lucchinetti C (2006) Pattern of T2 hypointensity associated with ring-enhancing brain lesions can help to differentiate pathology. *Neuroradiology* 48:143–149
- Hawkins CP, McLaughlin JE, Kendall BE, McDonald WI (1993) Pathological findings correlated with MRI in HIV infection. *Neuroradiology* 35(4):264–268
- Thurnher MM, Rieger A, Kleibl-Popov Ch et al (2001) Primary central nervous system lymphoma in AIDS: a wider spectrum of CT and MRI findings. *Neuroradiology* 43:29–35
- Johnson BA, Fram EK, Johnson PC, Jacobowitz R (1997) The variable MR appearance of primary lymphoma of the central nervous system: comparison with histopathologic features. *AJNR Am J Neuroradiol* 18:563–572
- Ernst TE, Chang L, Witt MD et al (1998) Cerebral toxoplasmosis and lymphoma in AIDS: perfusion MR imaging experience in 13 patients. *Radiology* 208:663–669
- Le Bihan D (1991) Molecular diffusion nuclear magnetic resonance imaging. *Magn Reson Q* 7:1–30
- Guo AC, Cummings TJ, Dash RC, Provenzale JM (2002) Lymphomas and high-grade astrocytomas: comparison of water diffusibility and histologic characteristics. *Radiology* 224:177–183
- Brightbill TC, Donovan Post MJ, Hensley GT, Ruiz A (1996) MR of toxoplasma encephalitis: signal characteristics on T2-weighted images and pathologic correlation. *J Comput Assist Tomogr* 20:417–422
- Kessler LS, Ruiz A, Donovan Post MJ, Ganz WI, Brandon AH, Foss JN (1998) Thallium-201 brain SPECT of lymphoma in AIDS patients: pitfalls and technique optimization. *AJNR Am J Neuroradiol* 19:1105–1109
- Skies DJ, Erdman W, Chang WE, Oz OK, Ware A, Fleckenstein J (2000) SPECT thallium-201 combined with toxoplasma serology for the presumptive diagnosis of focal central nervous system mass lesions in patients with AIDS. *J Infect* 40:274–281