ORIGINAL ARTICLE

MRI Findings of Intracranial Primary CNS Lymphoma in Immunocompetent Patients: A Malaysian Tertiary Hospital Experience

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ABSTRACT

Introduction: The present study aimed to characterize the MRI features of intracranial primary central nervous system lymphoma (PCNSL) in the Malaysian population, and to compare the findings with other population-based studies. **Methods:** Twenty-four patients with histologically confirmed PCNSL from 2008 to 2014 were identified. Eighteen patients had MRI images at presentation available for review. The images were reviewed by two radiologists, noting the number, size, location, signal characteristics, perilesional oedema and characteristics of enhancement of the lesions. **Results:** Ten patients had solitary lesions, while 8 patients had multiple lesions with a total of 31 lesions. The lesions were mostly located in the frontal lobe and basal ganglia. Most lesions were hypointense on T1 sequences, hyperintense on T2 sequences, with moderate to marked perilesional oedema. All lesions showed contrast enhancement. Five lesions demonstrated the 'notch sign', 1 lesion showed 'open-ring' pattern of enhancement and 1 lesion had a non-enhancing core. Seventeen lesions demonstrated an uneven enhancement pattern, mainly in lesions that are abutting the ventricular margins. **Conclusion:** MRI findings of patients with PCNSL in our population concur with other population-based studies. Enhancement patterns like the 'notch sign', 'open-ring', and uneven enhancement are not uncommon in PCNSL.

Keywords: Neuroimaging, Central nervous system lymphoma, Immunocompetent, Notch sign, Open ring

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INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is firstly decribed by Valvamis et al. in 1976 (1,2). It is a rare form of extranodal non-Hodgkin lymphoma and defined as isolated involvement of brain, leptomeninges, spinal cord or eyes in the absence of systemic lymphoma. It accounts for 2-6% of all primary brain tumors and 1-2% of all non-Hodgkin lymphomas (3,4). Patients who are immunocompromised secondary to HIV, organ transplantation, or congenital immunodeficiency syndromes are at particular risk for developing PCNSL. However, the majority of patients are immunocompetent, and approximately 95% of PCNSL in immunocompetent patients are diffuse large B-cell lymphomas (DLBCL) (3,5).

The prognosis of PCNSL is poor if there is no treatment given to the patients (6). However, the mean survival times of PCNSL patients can be improved significantly with the combination of chemotherapy and radiation therapy (7,8). This is because PCNSL is sensitive to both regimens. In addition to the mean survival times, the median survival times of patients were also improved between 33-60 months (9,10), and young age and good performance status are favorable prognostic factors (3,4). Brain biopsy is the gold standard for the diagnosis of PCNSL, and should be performed prior to any therapy. Initiation of corticosteroid treatment before biopsy in an attempt to decrease cerebral oedema can lower the diagnostic yield of the procedure, since steroids are lympholytic. If the correct diagnosis is suggested early based on imaging criteria, corticosteroid treatment can be held off or alternative agents such as mannitol or hypertonic saline can be utilized (11). This will facilitate attempts at biopsy and subsequently allow for proper management to be carried out promptly.

There are several typical imaging features of intracranial PCNSL which are namely iso- to hypointense on T1-weighted images, iso- to hyperintense on T2-weighted images with marked contrast enhancement and perilesional oedema (12). Other less common

imaging features that are associated with intracranial PCNSL include the 'notch sign' and 'open-ring' enhancement. The former is defined as an abnormally deep depression at the tumor margin, while the latter refers to an incomplete ring of enhancement (8). The present study aims to characterize MRI features with the inclusion of 'notch sign' and 'open ring' enhancement in the diagnosis of intracranial PCNSL among the immunocompetent patients in Malaysia. By identifying the unique MRI features in our local population, and comparing the findings with other population-based studies, we aim to propose a more comprehensive MRI protocol including advanced imaging techniques that have been used in other countries as a problem-solving tool in the diagnosis of intracranial PCNSL.

MATERIALS AND METHODS

The Medical and Research Ethics Committee of Malaysia approved this retrospective study with waiver of informed consent. Twenty-four patients (14 men and 10 women) with histologically confirmed PCNSL were referred to Ampang Hospital, Malaysia from 2008 to 2014, ranging from 21 years to 68 years of age (mean 49 years). All patients were negative for Human Immunodeficiency Virus (HIV). Of the 24 patients, 18 were diagnosed with intracranial PCNSL, and had magnetic resonance imaging (MRI) images at presentation available for review. Clinical features, histologic diagnosis, treatment regimen, and clinical outcomes were obtained from the patients' clinical records. Progression-free survival (PFS) was used as the endpoint of the patients, which was calculated from the date of diagnosis to the date of progression, relapse or death; or to the date of last follow-up.

As the patients have been referred from all over Malaysia, imaging was performed on different MR scanners with field strength of 0.5-1.5 T. All MRI studies had fluid-attenuated inversion recovery (FLAIR), T1- and T2-weighted images, and post contrast T1-weighted images. A neuroradiologist and an experienced radiologist independently analyzed the images, and all of the disagreements were resolved with consensus. All lesions were reviewed noting the number, size, location, signal characteristics, perilesional oedema and characteristics of enhancement. The presence of haemorrhage, necrotic components or calcifications was also examined.

The degree of oedema was rated in relation to the size of the contrast-enhancing lesion on T1-weighted images (mild, moderate or marked). Contrast enhancement was rated for intensity (mild/marked), pattern of enhancement (homogeneous/heterogeneous), and other characteristics ('ring-like'/'notch sign') via visual assessment. Necrotic components were defined by areas that are hypointense on T1-weighted images and FLAIR, and hyperintense on T2-weighted images.

RESULTS

Clinicopathologic and neuroimaging features of the 18 patients with intracranial PCNSL and available MRI images at presentation are summarized in Table I.

Demography

The patients age ranged from 21 to 63 years, with mean age of 48 years and median of 51.5 years. The commonest age group was 50 – 60 years. There were 11 male patients and 7 female patients.

Clinical features

Most of the patients in the present study presented with hemiplegia (39%), followed by seizures (22%) and disturbance of intellectual function or behavioral problems (17%). Other clinical signs at presentation included headache (2 cases), and blurring of vision (2 cases).

Histopathology

Fourteen patients (78%) had diffuse large B-cell lymphoma. There were only 3 cases of T-cell lymphoma, and 1 case was reported with non-specified Non-Hodgkin lymphoma.

Neuroradiological Findings

Ten patients had solitary lesions, while 8 patients had multiple lesions (2 lesions in 6 patients, 4 lesions in 1 patient and 5 lesions in 1 patient), with a total of 31 lesions. The lesions were mostly located in the frontal lobe and basal ganglia (8 lesions respectively), followed by the temporal lobe (4 lesions). Thirteen lesions were found abutting the ventricular margin and 10 lesions were in contact with the meningeal surface.

On T1 sequences, 18 lesions (58%) were hypointense, 9 lesions (29%) were isointense, and 3 lesions were hyperintense (10%). On T2 sequences, 17 lesions (55%) were hyperintense, and 13 lesions were isointense (42%) (Fig. 1). One cerebellar lesion was too small for T1 and T2 signal characterization, and it can only be seen in the post contrast images. Out of 31 lesions, only 3 lesions had necrotic components and 1 lesion had haemorrhagic changes. Perilesional oedema was

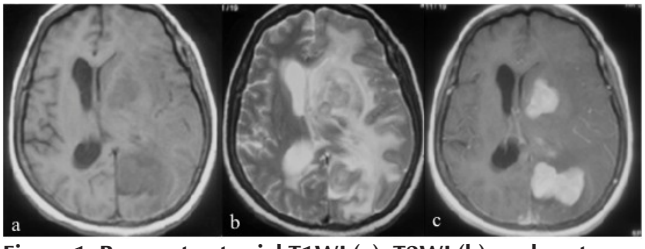

Figure 1: Pre-contrast axial T1WI (a), T2WI (b), and post-contrast axial T2WI (c) show the typical appearance of PCNSL in a patient with 2 lesions, one in the left basal ganglia and another in the left occipital lobe. These markedly enhancing lesions are hypointense on T1WI and hyperintense on T2WI, and are associated with marked perilesional oedema

Table I: Summary of clinicopathologic and neuroimaging features

Pt.	Age/ Sex	No. of lesion	Location	Presentation	HPE	T1	T2	Enhancement	Oedema	Necrosis	Hemorrhage	Meningeal enhancement
1.	63/M	2	R basal ganglia (V) L frontal (V)	Hemiplegia	DLBCL	Hypo	Iso	++	+++	N	N	N
						Hyper	Hyper	+	-	Y	Yes - rim	N
2.	62/M	2	R basal ganglia (V) L temporal	Poor memory	DLBCL	Hyper	Iso	++	+++	N	N	N
						Hypo	Iso	++	+	N	N	Y
3.	57/F	2	L basal ganglia (V) L parieto-occip-ital (V)	Seizure	DLBCL	Hypo	Iso	++	+++	N	N	N
						Hypo	Iso	++	+++	N	N	Y
4.	40/F	1	L frontal	Headache	NHL (NOS)	Hypo	Iso	++	+++	N	N	Y
5.	48/F	2	L parieto-occip-ital (V)	Hemiplegia	DLBCL	Iso	Iso	++	+++	N	N	N
			R parietal (V)			Iso	Iso	++	+	N	N	N
6.	55/M	1	R basal ganglia (V)	Hemiplegia	DLBCL	Hypo	Iso	++	++	N	N	N
7.	21/M	1	L subependymal (V)	Headache	T-cell lym-phoma	Iso	Iso	++	+	N	N	N
8.	53/F	2	R occipital	Seizure	DLBCL	Iso	Iso	++	++	Y	N	Y
			R temporal meninges			Iso	Hyper	++	-	N	N	Y
9.	40/M	4	R temporal (V) L temporal	Poor memory	DLBCL	Hypo	Hyper	++	+++	N	N	N
			L temporal			Hypo	Hyper	++	+++	N	N	N
			R frontal			Hypo	Hyper	++	++	N	N	N
						Hypo	Hyper	++	+	N	N	N
10.	49/M	1	R fronto-parietal	Seizure	DLBCL	Hyper	Hyper	++	+++	N	N	N
11.	48/M	2	R frontal (V)	Abnormal behavior	DLBCL	Hypo	Hyper	++	+++	N	N	Y
			L frontal			Hypo	Hyper	++	+++	Y	N	N
12.	53/F	1	R basal ganglia (V)	Hemiplegia	DLBCL	Iso	Iso	+	+++	N	N	N
13.	51/M	1	R basal ganglia (V)	Hemiplegia	DLBCL	Hypo	Hyper	++	+++	N	N	N
14.	52/M	1	L basal ganglia	Blurring of vision	DLBCL	Iso	Iso	++	++	N	N	N
15.	28/F	1	L basal ganglia	Blurring of vision	T-cell lym-phoma	Hypo	Hyper	++	+++	N	N	N
16.	34/F	1	R frontal	Seizure	DLBCL	Iso	Hyper	+	+	N	N	Y
17.	53/M	5	Midbrain	Hemiplegia	T-cell lym-phoma	Hypo	Hyper	+	+	N	N	N
			Pons			Hypo	Hyper	+	+	N	N	N
			L Cingulate gyrus R frontal			Hypo	Hyper	+	+++	N	N	Y
			R cerebellum			Hypo	Hyper	++	+	N	N	N
						N/A	N/A	+	+	N	N	N
18.	59/M	1	R parietal	Hemiplegia	DLBCL	Iso	Hyper	++	+++	N	N	N

DLBCL - Diffuse large B-cells lymphoma, F - Female, HPE - histopathological examination, L - left, M - Male, N - No, N/A: not available, NHL - Non-Hodgkin Lymphoma, NOS - not otherwise specified, Pt. - Patient, R- Right, V- abutting ventricular system, Y - Yes, Enhancement + mild, ++ marked, Oedema – none, + mild, ++ moderate, +++ marked.

present in 29 lesions (94%), in which 9 cases had mild oedema, 4 cases with moderate oedema and 16 cases had marked oedema.

All 31 lesions showed contrast enhancement, 7 lesions (23%) were mildly enhancing while 24 lesions (77%) were markedly enhancing. Five lesions (16%) demonstrated the 'notch sign' and 1 lesion showed 'open-ring' pattern of enhancement (Fig. 2-5). Seventeen lesions (55%) showed uneven enhancement (Fig. 6). This pattern of enhancement was seen mainly in lesions that were abutting the ventricular margins.

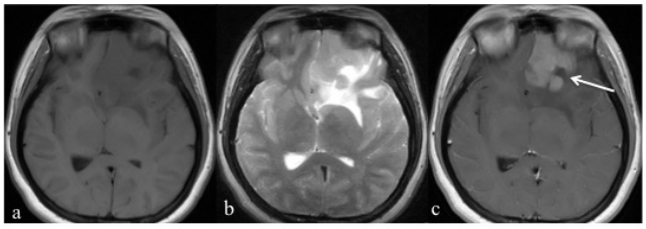

Figure 2: Pre-contrast axial T1WI (a), T2WI (b), and post-contrast axial T2WI (c) in a patient with lymphoma in the left frontal lobe. The 'notch sign' was demonstrated in the post-contrast image (arrow) as an abnormally deep depression at the margin.

Treatment regimens and progression-free survival (PFS)
Thirteen patients (72%) received DeAngelis chemotherapy protocol while another 3 patients (17%) received Hyper-CVAD chemotherapy protocol. Five patients received radiotherapy in addition to the chemotherapy. One patient succumbed to the disease before commencement of any therapy and 1 patient refused any treatment. At last follow up, 13 patients (72%) had died or experienced either progression or relapse. The median PFS was 16.0 months.

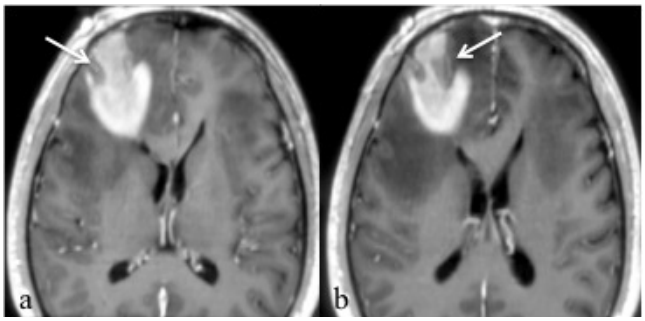

Figure 3: Post-contrast axial T1WI (a,b) demonstrates the 'notch sign' (arrows) at the margin of a markedly enhancing mass

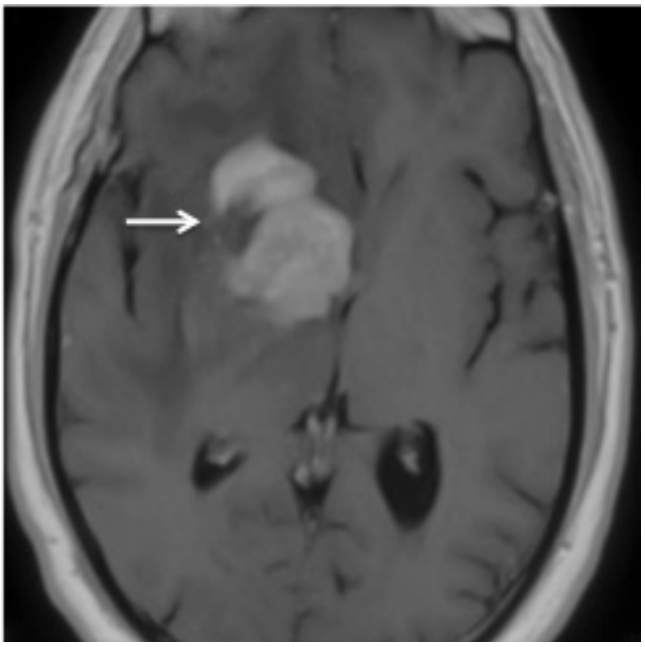

Figure 4: Post-contrast axial T1WI demonstrating the 'notch sign' (arrow) at the margin of a markedly enhancing mass

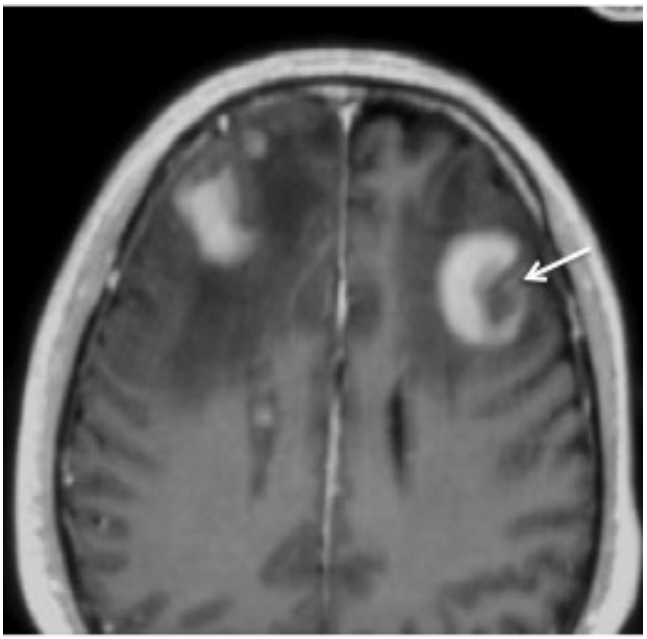

Figure 5: 'Open-ring' enhancement (arrow) on a post-contrast axial T1WI with a thick and non-uniform wall

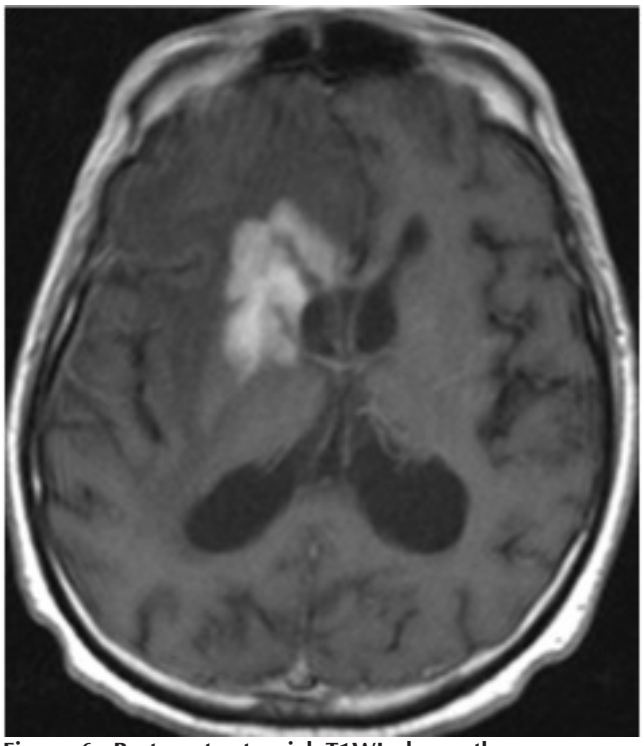

Figure 6: Post-contrast axial T1WI shows the uneven enhancement pattern in a right frontal periventricular mass

DISCUSSION

Intracranial PCNSL is potentially associated with a number of radiological presentations, and can occasionally mimic other brain tumours (meningioma, malignant glioma, brain metastases), inflammatory (multiple sclerosis, acute disseminated encephalomyelitis) or infectious (Toxoplasmosis encephalomyelitis) diseases (13). Therefore, the differentiation of PCNSL from other types of tumors and diseases is important because the management and prognosis varies from one to another. Prompt chemotherapy and radiotherapy can significantly improve the outcome in PCNSL patients (6).

Clinical findings alone cannot differentiate PCNSL from other intracranial lesions (7). As shown in the present study, most of the patients presented with hemiplegia and seizures. These clinical presentations differ from other cohorts, wherein patients often experienced headache, disturbance in intellectual function, and impairment of motivation (5,7,8). None of the patients in the present study presented with night sweats, fever or weight loss. These symptoms are rarely reported in PCNSL, but are rather usually associated with systemic non-Hodgkin lymphoma (5).

The mean age at diagnosis in the current study was 51.5, which is similar to that of other studies from China and Turkey (5,8). However, it is lower than the published data in Europe (4,14). It was found that males are more frequently affected with PCNSL compared to females at a ratio of 1.5. This finding corroborates with other studies, which reported the ratio of males to females

PCNSL patients between 1.2 to 1.7 (5,7,8,15,16). The frequency of multifocal lesions in PCNSL ranges from 0-50% (8), and it was reported in 44% of patients in the present study. The maximum number of lesions in a patient was five.

The current study confirmed that the frontal lobe and basal ganglia were the most frequent locations of intracranial PCNSL (4,7,8). Thirteen lesions (42%) were in contact with the ventricular surface, and only 3 lesions (10%) were located in the posterior fossa, which is consistent with the previous studies (8,14). There were no patients with lesions involving both sides of tentorium.

Majority of the lesions in the current study are hypo- to isointense to white matter on T1WI and iso- to hyperintense on T2WI, which are consistent with other published reports (3,4,7,8). Haemorrhage and necrosis are rarely reported in intracranial PCNSL lesions, and there is only 1 lesion with haemorrhage, and 2 lesions with necrosis in this study (4,17). Peritumoral oedema, a common feature of intracranial PCNSL, was observed in 94% of the lesions, mostly moderate to marked (1,8). This finding differs from the previous study, which reported a mild to moderate oedema in all of the evaluated lesions (8).

Contrast enhancement was observed in all lesions in the present study. In 24 of the 31 lesions, the enhancement was reported as intense. Majority of the lesions enhanced homogeneously. There were two specific enhancement patterns observed in the present study, which are the 'notch sign' and 'open-ring' enhancement. The 'open-ring' enhancement is highly specific to brain demyelination (18). However, the thick and non-uniform ring in PCNSL lesions allows differentiation from the thin and uniform ring in brain demyelination (8). The 'notch sign' is not an unusual enhancement pattern, and it was reported in 4 lesions in a study conducted by Zhang et al. (8), while 5 lesions with this enhancement pattern were observed in the present study.

Seventeen lesions showed uneven enhancement. In 11 of the 17 lesions, there was contact with a ventricular surface. Previously, Smirniotopoulos et al. described that PCNSL has a periventricular pattern of homogeneous "lamb's wool" appearance on contrast-enhanced CT images (19). The uneven enhancement pattern in an otherwise homogeneously enhancing lesion on MR images has not been described well previously. This appearance may be due to the heterogeneous architecture of PCNSL that is attributed by several factors such as variable cell density, neovascularization, and infiltration by immune cells (19-21).

Pattern of enhancement is a useful determinant in differentiating intracranial PCNSL from gliomas, as gliomas enhance heterogeneously with necrotic areas whereas PCNSL enhance homogeneously. Current advanced neuroimaging tools such as diffusion weighted imaging, spectroscopy, and dynamic susceptibility contrast-enhanced MRI have been suggested as problem-solving tools in the evaluation of PCNSL (22,23). In PCNSL, diffusion is more restricted with lower apparent diffusion coefficient (ADC) than gliomas. The relative minimum ADC (rADCmin) has been suggested to be an accurate differentiator of PCNSL, with a cut-off value of 0.722 (24).

On dynamic susceptibility contrast-enhanced MRI (DSCE-MRI), studies have shown that PCNSLs demonstrate lower regional cerebral blood volume (CBV) than other tumours. Magnetic resonance spectroscopy (MRS) can also help in the diagnosis of PCNSL, showing reduced N-acetylaspartate (NAA) peaks, elevated choline to creatine ratio, lipid peaks and lactate peaks. In the absence of necrosis, it is suggested that an increase in lipid is the most specific finding in intracranial PCNSL (24).

Although the present study has successfully demonstrated that the potential use of enhancement patterns in MRI assessment for diagnosis of intracranial PCNSL, a few limitations must be brought to attention. The study population is small with only 18 patients, as the disease is rare with worldwide incidence of approximately 51 cases per 10,000,000 per year (25). Furthermore, the study focused solely on intracranial PCNSL lesions. All confirmed PCNSL patients in this study were HIV-negative. However, other factors which may impair the patient's immune status such as diabetes mellitus were not assessed as it was beyond the scope of the study.

In the present study, most of the patients underwent MRI assessment at different Malaysian hospitals prior to referral to the tertiary hospital. The use of different MRI machines (ranging from 0.5 T to 1.5 T) and protocols may lead to the inconsistency of determining the features during MRI assessment, and this discrepancy may limit the ability to analyze the pattern of PCNSL precisely among the patients in the present study. This is the first study that describes uneven enhancement pattern and the findings have a number of important implications for future practice. Large population of patients should be incorporated in future analysis to provide more definitive evidence on the specificity of the enhancement patterns like the 'notch sign', and other advance neuro-imaging techniques in the diagnosis of intracranial PCNSL.

CONCLUSION

MRI findings at presentation of patients with intracranial PCNSL in with the present study were in parallel with other population-based studies. The patients in this study were mostly male in the 5th to 6th decade, with single or multiple contrast enhancing lesions which show predilection to the frontal lobe and basal ganglia.

These lesions are typically hypo- to isointense on pre-contrast T1WI and iso- to hyperintense on T2WI, with moderate to marked perilesional oedema, and homogeneous contrast enhancement. Enhancement patterns like the 'notch sign', 'open-ring', and uneven enhancement are not uncommon in intracranial PCNSL. Recent studies have indicated the value of MR diffusion, perfusion and proton spectroscopy in the diagnosis of intracranial PCNSL. Findings consistent with PCNSL include diffusion restriction, relative hypoperfusion, increase Cho/Cr, Cho/NAA, decreased NAA/Cho, NAA/Cr, and presence of lactate and lipid peaks.

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