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The added value of advanced neuro-imaging (MR diffusion, perfusion and proton spectroscopy) in diagnosis of primary CNS lymphoma

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KEYWORDS

Primary central nervous system lymphoma;
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Abstract *Introduction:* Primary CNS lymphoma is difficult to diagnose with conventional imaging modalities. Magnetic resonance proton spectroscopy, dynamic susceptibility contrast DSC perfusion and diffusion weighted images have been recently investigated as a problem-solving tool for evaluation of primary CNS lymphoma with favorable results.

Aim of the work: To assess the value of advanced neuro-imaging (MR diffusion, perfusion and proton spectroscopy) in diagnosis of primary CNS lymphoma.

Patients and methods: Five adult patients with suspected primary CNS lymphoma (as suggested by clinical or conventional imaging techniques) were prospectively studied by magnetic resonance proton spectroscopy, dynamic susceptibility contrast DSC perfusion and diffusion weighted images aiming to confirm the suspected diagnosis. The examinations were done on 1.5T machines using diffusion weighted, dynamic susceptibility contrast perfusion and chemical shift CSI imaging sequences.

Results: Regarding DWI, all patients show low ADC values ranging from 0.61 to 0.67×10^{-3} mm^2/s with a mean ADC value of $0.63 \pm 0.025(SD) \times 10^{-3}$ mm^2/s, regarding the DSC perfusion. The max rCBV ratios are ranging from 0.23 to 1.52 with a mean ratio of $1.14 \pm 0.54(SD)$. Regarding

Abbreviations: PCNSL, primary central nervous system lymphoma; SCI, chemical shift imaging; DSC, dynamic susceptibility contrast; DWI, diffusion weighted images.

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the MRI spectroscopy Cho/Cr ratios are ranging from 1.9 to 63 with a mean ratio of 19.16 ± 26 (SD), Cho/NAA ratios are ranging from 3.7 to 50 with a mean ratio of 14.8 ± 19.8, NAA/Cr ratios are ranging from 0.09 to 1.6 with a mean ratio of 0.72 ± 0.59, NAA/Cho ratios are ranging from 0.02 to 0.3 with a mean ratio of 0.19 ± 0.1 Lactate peak was found in three cases. Lipid peak was found in two cases. Myo inositol peak was found in one case.

Conclusions: Restricted diffusion, relative hypo perfusion, increased Cho/Cr, Cho/NAA, decreased NAA/Cho, NAA/Cr and presence of lactate or lipid peaks are consistent imaging finding in CNS lymphoma.

1. Introduction

Primary central nervous system lymphoma (PCNSL) is defined as isolated intra axial brain and spinal cord involvement with absence of primary tumor foci at any other sites of the body, primary lymphomatous infiltration of the CNS occurs in healthy populations, AIDS, post organ transplantation patients and also in patients receiving chemotherapy. It is considered as a rare disease in all categories with increased incidence in the latter groups.[1] The role of advanced neuro imaging is not limited only to provide anatomic details but also helps for proper diagnosis of the disease, the value of the advanced magnetic resonance imaging techniques, such as MR diffusion, DSC perfusion imaging and MR proton spectroscopy, in the diagnosis of adult CNS lymphoma will be discussed in this study.[2]

The ratio of PCNSL among malignant tumors of the brain and spinal cord is ranging from 1% to 6% and of all extra-nodal non-Hodgkin's lymphomas are ranging from 3% to 5%.[3,4] The incidence is 0.5:1/000,000/year so it is considered as a rare occurrence.[5] The clinical and imaging features of PCNSL differ according to the immunological status of the patients,[6] this study is only limited to the immunocompetent patients.

The most predominant pathological type of PCNS lymphoma in the immunocompetent patients is the Non-Hodgkin's B-cell variant.[7] B-cell type of primary CNS lymphoma is more frequent in male patients and occurs mainly among elder age groups of 50–60 years.[7] The most common symptoms at the initial presentations of the disease include alteration and deterioration of mental status, sub-acute hemiparesis, headache, nausea, cerebellar manifestations including ataxia, cranial nerve palsies, and visual disturbances.[7,8]

Other tools used for diagnosis of the PCNLS include Cytological CSF analysis, which only diagnoses about less than half of patients with primary CNS lymphoma.[8] Stereotactic biopsy for pathological diagnosis of cerebral lymphoma is the most accurate method however specimens may be insufficient for diagnosis yet still both techniques are invasive methods and have multiple complications related to the intervention.[8]

The common initial radiological presentation of lymphomatous lesions is a large sized intra axial mass with peri focal edema and mass effect.[9] The use of steroids medication as attempts to reduce the peri focal edema of the lesion and relief pressure effects on the brain tissue may compromise and interfere with the trails of stereotactic brain and spinal needle biopsies or CSF analysis.[10] Diagnosis of PCNSL by image based interpretation is crucial to avoid resection which is not improving the prognosis and survival rate of the patients as well as to avoid false negative results which may be seen in the follow up images.[11]

Primary CNS lymphoma may arise from any region of the brain however; the most common site of origin is the deep hemispheric periventricular white matter. It can arise also from the Corpus callosum, orbits, cranial nerves and cerebellum.[12]

Most of the lymphomas appear in conventional MR imaging techniques as hypo or iso intense to gray matter on T1-WI, variable signal intensities yet predominantly hypo intense on T2-WI and show avid enhancement after contrast administration.[13] The MR imaging findings of PCNS lymphomas are extremely variable and intermingled with MR imaging findings of other intracranial tumors regarding the distribution, signal intensity pattern, peri focal edema, mass effect and enhancement pattern such as high grade gliomas, deposits or meningiomas. Therefore, the proper diagnosis of CNS lymphoma is difficult on conventional MRI.[14]

Diffusion MR imaging, diffusion detects the water molecules' random motion as they diffuse through the extra-cellular space; tumor diffusion is considered as a marker for tumor cellularity.[15] CNS lymphomas are highly cellular tumors; diffusion restriction is one of their main features, making them appear hyper-intense on DWI and hypo-intense on ADC maps.[16]

Perfusion MR imaging, perfusion refers to oxygen and nutrients' delivery to the cells via capillaries in the biologic tissue (tumors); with calculation of cerebral blood flow, cerebral blood volume, mean transit time, and time to peak, cerebral lymphomas show relatively low rCBV values compared with similar appearing tumors.[17]

MR spectroscopy monitors biochemical changes in tumors depending upon the chemical shift phenomena using proton (hydrogen) nuclei. In PCNSL proton MR spectroscopy shows high Cho/Cr ratios and elevated lipid, lactate and choline peaks, reduced NAA peaks are also detected.[18,19]

2. Aim of the work

To assess the value of advanced neuro-imaging (MR diffusion, perfusion and proton spectroscopy) in diagnosis of primary CNS lymphoma.

3. Methods

3.1. Study population

Between December 2011 and December 2012, patients who presented to the Neuro Surgery Unit in Alexandria Main

University Hospital with suspected primary CNS lymphoma were referred to the Radio Diagnosis Department for imaging assessment. Five adult patients (3 males and 2 females) age ranged from 27 to 82 years (median age 57 years) presented with one of the following clinical presentations focal neurological deficit, alteration of mental status, hemiparesis, increased intracranial pressure, and seizures.

The presence of specific altered attenuation or signal pattern as iso dense to hyper dense lesions on CT scan and iso to hypo intense lesions on T2-weighted MRI. Specific location, central, hemispheric or periventricular cerebral white matter, Frontal lobe, basal ganglia, brain stem or cerebellum also superficial location adjacent to the meninges. Enhancement pattern as homogeneous or ring-like enhancement is driving attention to further advanced neuro imaging evaluation.

3.2. Imaging techniques and analysis

MR imaging was performed using Siemens Avanto 1.5 MR system with a standard head coil. Conventional MRI study was done with conventional T2 [fast spin echo (FSE), fluid attenuated inversion recovery (FLAIR)], T1 and susceptibility Weighted SWI sequences, with T1 post intravenous administration of paramagnetic contrast material (gadobutrol, 0.1 mmol/kg, Magnevist, Schering, Germany).

3.3. Diffusion analysis

The DWI study was performed with a T2-weighted, echo-planar spin-echo sequence EPI (TR 3400, TE 100, matrix 192×192, slice thickness 5 mm, gap 30%) with a duration of 120 s and $B = 0$, $B = 500$, and $B = 1{,}000$. Isotropic maps of the ADC maps were calculated, and the lowest ADC was measured in the lesion core.

3.4. Perfusion analysis

The standard PWI protocol was performed with a T2-weighted echo planar spin-echo sequence EPI (TR 1.480, TE 30, matrix 128×128, slice thickness 5 mm, gap 0, number of scans 50, IPAT2 Grappa 128 epi factor) with duration of 81 s. Nineteen images per second were acquired during the passage of a bolus of 0.1 mmol/kg of gadobutrol, injected with an automatic injector at a flow velocity of 5 ml/s through an 18- to 20-gauge needle cannula, followed by irrigation of 20 ml saline solution. Post processing was performed with a dedicated software package (Syngo neuro perfusion evaluation). Color maps of the cerebral blood volume were obtained, and the maximum regional cerebral blood volume (rCBV) was calculated by placing the region of interest ROI in the solid areas showing the highest color intensity. Data were then compared with those of the normal-appearing contralateral or ipsilateral white matter and expressed as a ratio of rCBV [ratio = rCBV (lesion)/rCBV (normal appearing white matter)].

3.5. Spectroscopy analysis

MR spectroscopy multi-voxel 2D CSI was performed with an echo time of intermediate TE (135) (TR 1500, FOV 160 mm, acquisition time 7 min 34 s) to evaluate the levels of choline (Cho), creatine (Cr), N-acetyl aspartate (NAA), lactate and lipids. Also we acquired data at short TE (30) to evaluate myo-inositol (MI) using a Point Resolved Spectroscopy (PRESS) Sequences. The size and position of the region of interest ROI were determined by examination of the MR images in all three dimensions (Sagittal, Coronal and Transverse planes), the aim is to include the largest volume of the tumor, peritumoral area as well as the normal appearing brain within the region of interest as much as possible and to exclude bone, air, and subcutaneous fat (the regions with large variations in magnetic susceptibility). Appropriate automatic shimming achieved by using 4–8- HZ line width, 1-kHz spectral width, and Water suppression using the CHESS technique (chemical shift selective saturation) were done and post processing performed with automated software package (Syngo spectroscopy evaluation).

3.6. Pathological analysis

The diagnoses were confirmed by pathology. Routinely processed paraffin-embedded tissues were cut and stained with the conventional H&E stain and reticulin stain. Sections on coated slides were submitted to immunohistochemistry for CD20, CD3, pancytokeratin and S-100. Both the primary antibody and the detection kit were purchased from Lab Vision Corporation (Neo Markers, USA). Immunohistochemical staining was performed using an avidin–biotinylated immunoperoxidase methodology.

4. Results

Patient's demographic and conventional MRI imaging data are demonstrated in Table 1. Advanced MRI imaging data are demonstrated in Table 2. Conventional MRI showed central location of the lesion for four patients and peripheral cortical and sub cortical location with central extension for one patient (Table 1; case 3) (Fig. 1D), multiple lesions are noted in four patients (Fig. 2), single lesion is noted in one patient (Table 1; case 2) (Fig. 3), low signal intensity to gray matter within the lesions in T2 weighted images found in three patients, T2 iso intense signals found in one patient (Table 1; case 3), high T2 signal intensity found in one patient (Table 1; case 4), intense enhancement noted in four patients (Fig. 3A), and moderate rim enhancement noted in one patient (Table 1; case 5).

Table 1 Patient demographic data and conventional MRI image findings.

Case no.	Sex	Age (years)	T2 signal pattern	Location	Number	Enhancement
1	M	27	Hypo-intense	Central	Multiple	Intense
2	M	39	Hypo-intense	Central	Single	Intense
3	F	65	Iso-intense	Peripheral	Multiple	Intense
4	M	82	Hyper-intense	Central	Multiple	Intense
5	F	57	Hypo-intense	Central	Multiple	Moderate

Table 2 Patient demographic data and advanced MRI neuro-image findings.

Case no.	Age (years)	Sex	ADC ($\times 10^{-3}$ mm^2/s)	rCBV	Perfusion	Cho/Cr	Cho/NAA	NAA/Cr	NAA/Cho	Lac	Lipid	MI
1	27	M	0.61	1.12	Decreased	24	50	0.09	0.02	Yes	Yes	No
2	39	M	0.62	0.23	Deceased	63	10	1.6	0.3	No	No	No
3	65	F	0.67	1.38	Increased	1.9	3.7	0.5	0.26	Yes	Yes	No
4	82	M	0.62	1.48	Increased	4.3	4.29	1	0.23	No	No	No
5	57	F	0.65	1.52	Increased	2.61	6.37	0.41	0.16	Yes	No	Yes

rCBV, relative cerebral blood volume; ADC, apparent diffusion coefficient; NAA, N acetyl aspartate; Cr, creatine; Cho, choline; MI, myo inositol; Lac, lactate.

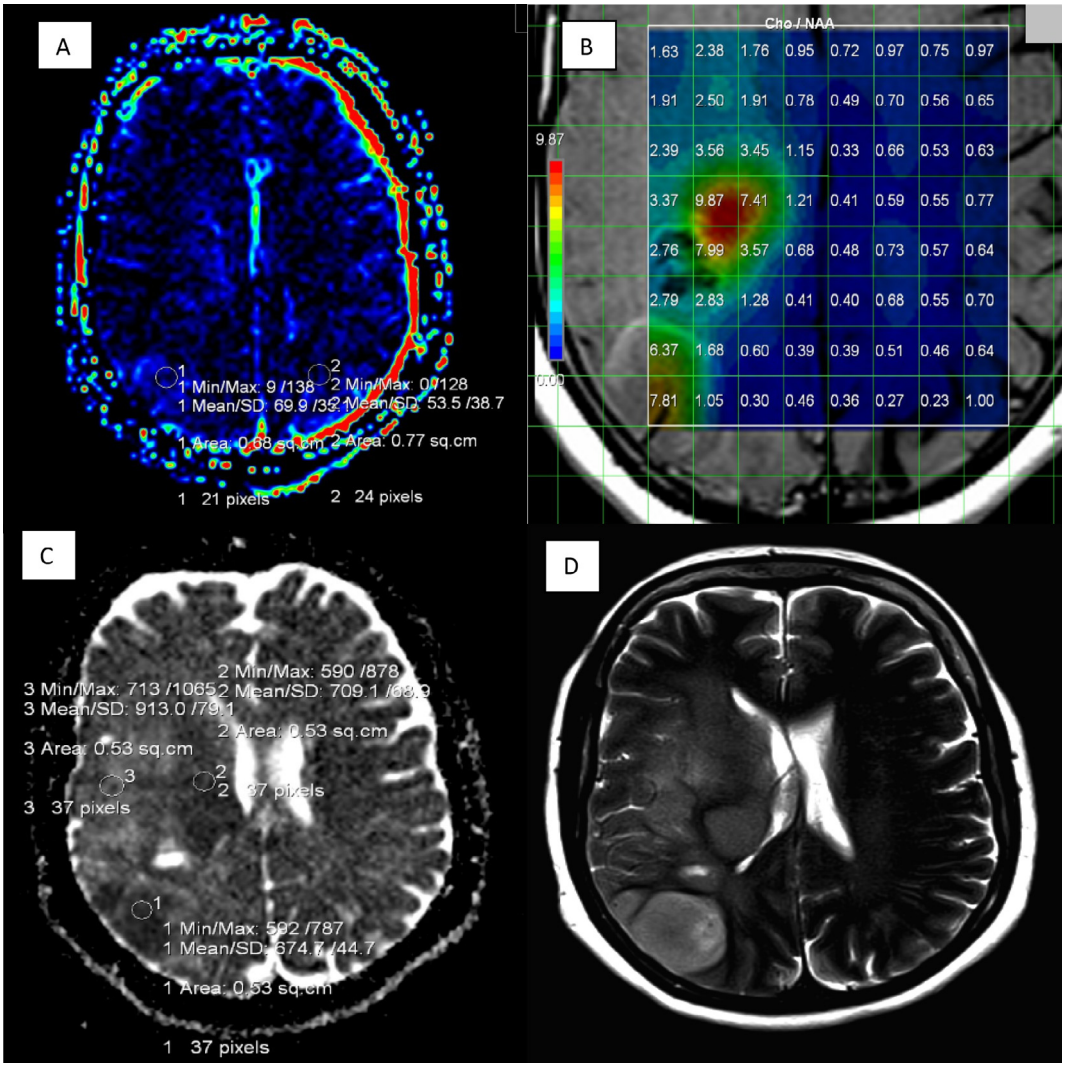

Figure 1 A 65 year old female with well infiltrative right fronto-parietal lesion. (A) rCBV color perfusion map shows right parietal cortical area of relative hyper perfusion. (B) Color intermediate echo spectroscopic map with right frontal para falcine foci of high Cho/NAA ratios (red colored). (C) Diffusion weighted image shows foci of low ADC values with profound restriction. (D) T2 W image shows iso intense to gray matter infiltrative right fronto-parietal lesion.

Advanced neuro-imaging data. Regarding the diffusion weighted images and ADC values. All patients show low ADC values (Figs. 1C, 2A, 3B) ranging from 0.61 to 0.67×10^{-3} mm^2/s with a mean ADC value of $0.63 \pm 0.025(\text{SD}) \times 10^{-3}$ mm^2/s (Table 2; case 1 and 3). For the central lesions the range of ADC values is from 0.61 to 0.65×10^{-3} mm^2/s with a mean ADC value of $0.625 \pm 0.017 \times 10^{-3}$ mm^2/s, Slightly higher ADC value is noted for the peripheral lesion 0.67×10^{-3} mm^2/s (Table 2; case 3).

Regarding the perfusion weighted images the maximum relative CBV ratio in all patients is summarized in Table 2. The rCBV ratios are ranging from 0.23 to 1.52 with a mean. rCVB ratio of 1.14 ± 0.54(SD) (Table 2; case 2 and 5) (Fig. 1A), perfusion is decreased with max. rCVB below 1.2 in two cases

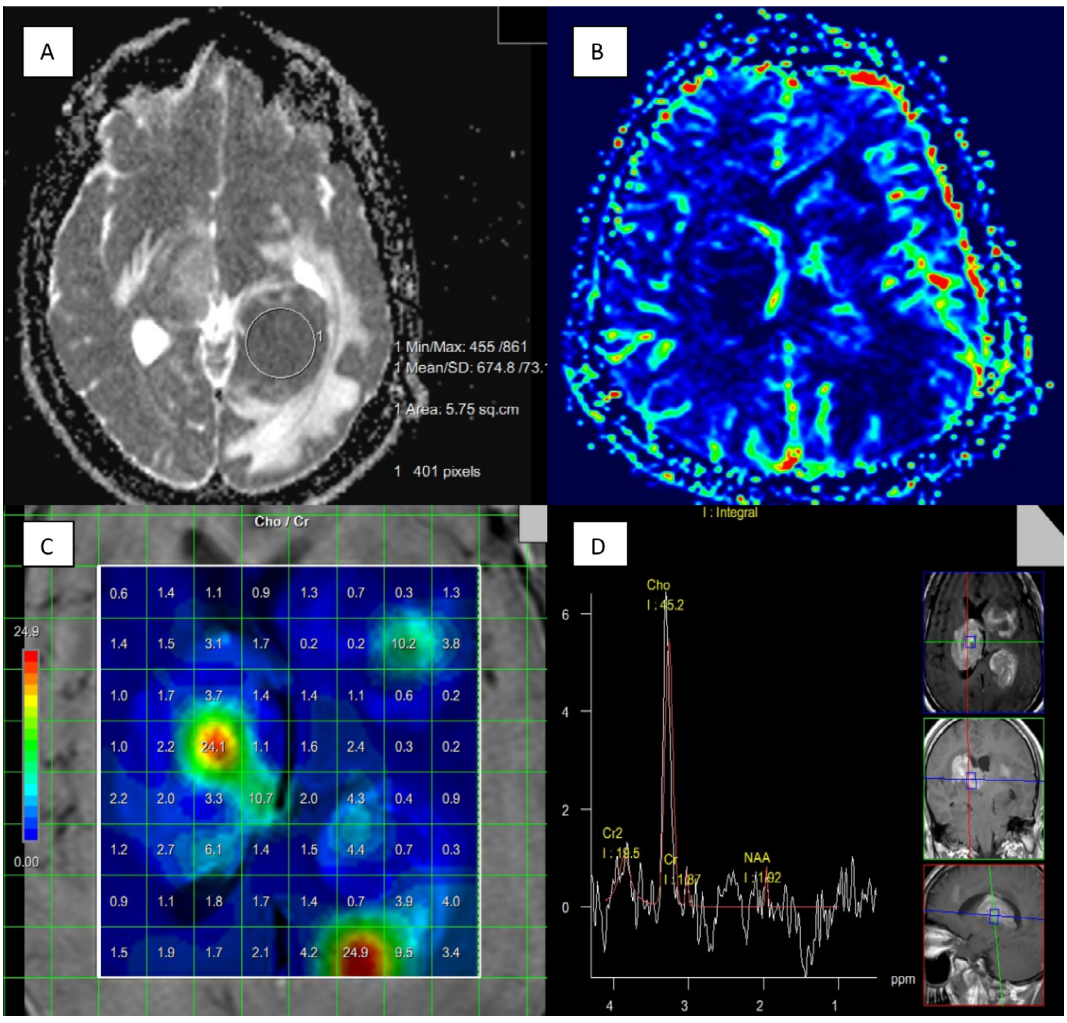

Figure 2 A 27 year old male with multiple lesions involving both cerebral hemispheres. (A) Diffusion weighted image shows large left parieto- occipital lesion with low ADC values and profound restriction. (B) rCBV color perfusion map for the same lesion shows area of relative hypo perfusion. (C) Color intermediate echo spectroscopic map shows foci of high Cho/Cr ratios (red colored). (D) Intermediate echo spectroscopy curve shows very high Cho levels and very low Cr &NAA levels with lactate peak (inverted peak at 1.33 ppm).

(case 1 and 2), relatively increased max. rCBV in three cases (case 3, 4 and 5) (Figs. 2B, 3C).

Regarding the MRI spectroscopy all the metabolic ratios are summarized in Table 2. Cho/Cr ratios are fluctuating, ranging from 1.9 up to 63 with a mean ratio of 19.16 ± 26 (SD), showing very high values in case (1 and 2) 24 and 63 respectively (Fig. 2C). Cho/NAA ratios are also ranging from 3.7 to 50 with a mean ratio of 14.8 ± 19.8 showing very high values in case (1 and 2) 50 and 10, respectively (Figs. 1B, 3D) .NAA/Cr ratios ranged from 0.09 to 1.6 with a mean ratio of 0.72 ± 0.59, NAA/Cho ratios ranged from 0.02 to 0.3 with mean ratio 0.19 ± 0.1, lactate peak is found in three cases (case 1, 3 and 5) (Fig. 2D). Lipid peak was found in two cases (case 1 and 3). Myo inositol peak is found in one case (case 5).

5. Discussion

Primary central nervous system lymphoma PCNSL is a rare aggressive neoplasm with increased incidence in the last decade among healthy populations and AIDS patients because of the newly developed medication that increases the survival rate of these patients, also among post organ transplant patients on immuno-suppressors and cancer patients on chemotherapy.[1] The diagnosis of CNS lymphoma is difficult by conventional MRI imaging. However, the proper diagnosis of CNS lymphoma and accurate differentiation from other intracranial mass lesions such as high grade gliomas, deposits, or meningiomas are important, because the management and prognosis are variable for these different types of tumors.[20]

Diffusion pattern of primary CNS lymphoma is low in most of the lesions reflecting high cellularity, they appear hyper intense on DWI along the different B values and hypo intense on ADC maps.[21] PCNSL lesions show evident diffusion restriction and have lower ADC values than similar appearing high-grade gliomas and deposits,[22] other lesions appearing with high signal intensity in DWI are acute ischemic stroke, pyogenic brain abscesses, intermediate grade gliomas, so they should be considered when diagnosing lymphoma.[22]

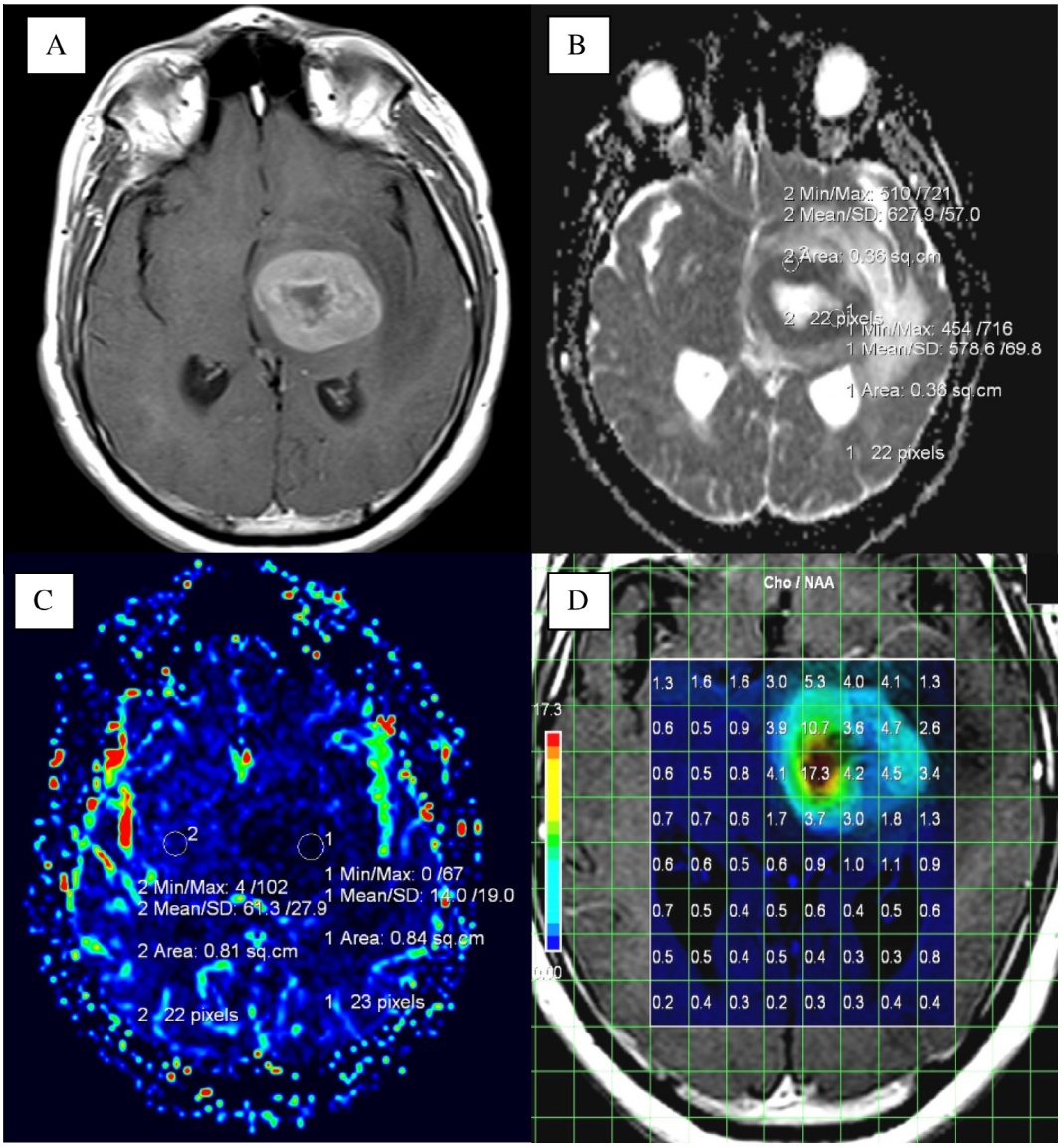

Figure 3 A 39 year old male with left deep parietal lesion. (A) Contrast enhanced T1 images show intensely enhancing left deep parietal lesion with necrotic core. (B) Diffusion weighted image shows thick peripheral rim of low ADC values and profound restriction. (C) rCBV color perfusion map for the same lesion shows area of manifest hypo perfusion. (D) Color intermediate echo spectroscopic map shows area of high Cho/NAA ratios (red colored).

Dynamic susceptibility contrast perfusion images measuring max. relative cerebral blood volume (rCBV) ratio are crucial for diagnosis of PCNS lymphomas, max. relative CBV measured in tumor tissue and it shows relatively lower values in lymphomas than in other brain malignancies. This important finding may differentiate high grade gliomas and deposits from lymphomas.[23]

PCNSL spectroscopic analysis shows variable spectral presentations with the presence of multiple zones of transitions between normal brain and tumor tissues. MR spectral pattern in PCNSL shows decreased NAA/Cho, NAA/Cr and increased Cho/Cr, Cho/NAA ratios; in few patients Cho was the only observable metabolite, others show decreased NAA level. Several patients had lactate, lipid, or both within the evaluated region of interest.[18]

Our results revealed that the rate of diffusion of CNS lymphomas, as represented by ADC value numbers, was significantly low, ADC values ranging from 0.61 to 0.67×10^{-3} mm^2/s with a mean ADC value of $0.63 \pm 0.025 \times 10^{-3}$ mm^2/s. In a study by Guo et al.,[24] the mean ADC of CNS lymphoma was $0.87 \pm 0.27 \times 10^{-3}$ mm^2/s, whereas the mean ADC of high grade astrocytoma was $1.21 \pm 0.35 \times 10^{-3}$ mm^2/s. Results of other studies[25] on this issue have revealed higher ADCs, up to $1.37 \pm 0.52 \times 10^{-3}$ mm^2/s. These findings were matching with our results of diffusion weighted MR pattern and ADC map analyses. Lymphomas were hyper intense to gray matter on diffusion-weighted images and relatively isointense to hypointense on ADC maps, these findings are attributed to low diffusivity.[24]

In this study, the results showed that the maximum rCBV ratios were less than 1.2 in two patients and more than 1.2 in other three patients. These results (mean value: 1.14 ± 0.54) are similar to the previous reports (mean values: 1.10–2.48).[25] These findings are different from other tumors such as high grade gliomas (mean values: 4.03–7.32) or metastasis (mean values: 4.68–5.27) or meningiomas (mean value: 8.02–10.58) with high max. rCBV ratios.[26] Sugahara et al. reported that cerebral lymphomas had a tendency to have lower rCBV values in 1999.[28] Hakyemez et al.[27] reported that the rCBV ratios of lymphomas were lower than those of high grade gliomas in 2006. Avid enhancement without higher rCBV ratios in lymphoma is attributed to destruction of the blood brain barrier without neovascularization in contrast to the avid contrast enhancement with neovascularization in high grade gliomas.[26]

In this study MR spectra with PCNSL consisted of increased Cho/Cr with mean ratio 19.16 ± 26, Cho/NAA with mean ratio 14.8 ± 19.8 and decreased NAA/Cho with mean ratio 0.19 ± 0.1 and NAA/Cr with mean ratio 0.72 ± 0.59, high lipid and lactate peaks, unexpected finding with the presence of myo inositol peak in one patient; These ratios are matching with PCNSL patients reported in literatures,[29] elevated lipid, Cho and decreased NAA ratios may help in differentiating between high grade glioma and lymphoma.[18,29] The increase in Cho likely results from high mitotic activity, increased cell turnover rate and the dense cellularity of lymphomas.[29] The lipid signals related to fatty acyl molecules were released during membrane breakdown.[30] The spectroscopic patterns seen in PCNSL are similar to high grade glioma. However, increasing ratios of Cho/Cr, Cho/NAA or decreasing NAA/Cho and NAA/Cr in PCNSL are related to tumor progression and possibly increased aggression rather than increased tumor grade.[31]

6. Conclusion

Advanced MR imaging techniques add more characteristic findings for the diagnosis of CNS lymphoma that may help in the differentiation of CNS lymphomas from other CNS malignancies. Diffusion restriction, relative hypo perfusion, increased Cho/Cr, Cho/NAA, decreased NAA/Cho, NAA/Cr as well as the presence of lactate and lipid peaks, these findings are consistent imaging findings in CNS lymphoma.

Conflict of interest

None declared.

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