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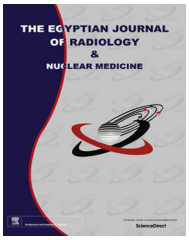

ORIGINAL ARTICLE

MR Spectroscopy evaluation of white matter signal abnormalities of different non-neoplastic brain lesions

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KEYWORDS

MR Spectroscopy;
White matter;
Non-neoplastic

Abstract *Objectives:* Our aim was to evaluate the efficacy of MR Spectroscopy in characterization of white matter signal abnormalities diagnosed by MRI detect changes in different metabolites and peaks of inflammation.

Patients and methods: 93 patients (49 females and 44 males) age ranging from 2 to 63 years with average (37 ± 2.34 years) presented with white matter hyperintense lesions on T2 and T2 FLAIR and/or contrast enhanced T1WI diagnosed on MRI are included our study.

Results: In Infectious group: Average Cho/NAA ratio: 0.79 ± 0.19, Cho/Cr ratio: 0.95 ± 0.17, NAA/Cr 1.89 ± 0.69, in inflammatory group Cho/NAA ratio: 0.65 ± 0.15, Cho/Cr ratio: 0.98 ± 0.29, Average NAA/Cr ratio 1.69 ± 0.19. In ischemic group: Average Cho/NAA ratio: 0.83 ± 0.09, Cho/Cr ratio: 0.81 ± 0.23, Average NAA/Cr 1.54 ± 0.39, in metabolic group: Average Cho/NAA ratio: 0.57 ± 0.13, Cho/Cr ratio: 0.76 ± 0.26; NAA/Cr ratio was 1.73 ± 0.44, in mitochondrial group, Average Cho/NAA ratio: 0.62 ± 0.19, Cho/Cr ratio: 0.54 ± 0.14, NAA/Cr ratio was 1.49 ± 0.59, in inherited dysmyelinating; Cho/NAA ratio: 0.51 ± 0.17, Cho/Cr ratio: 0.63 ± 0.13; Average NAA/Cr ratio was 1.87 ± 0.65. Glutamate and myoinositol peak raised in inflammatory, infectious, metabolic, inherited, and ischemic group mainly in the acute and subacute stage. Amino acids and succinate peak specifically are raised in brain abscesses.

Conclusion: MRS is a noninvasive additional MRI technique to define the nature of non-neoplastic brain lesions. Together with image analysis, it may be the key to etiologic diagnosis or, at least, definition of the group where the lesion is classified, by detecting changes in different metabolites and peaks of inflammation.

1. Introduction

White matter lesions may be demyelinating with loss of normally formed myelin, classified as infectious, inflammatory, metabolic, vascular, neoplastic or dysmyelinating: inherited

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Table 1 Pathology classification of white matter diseases.

White matter lesions:	Infectious (33): 35.48%	TB: 6
Demyelinating:		Cysticercosis: 4
Infectious		Encephalitis:14
Inflammatory		Encephalitis with ventriculitis: 2
ischemic		Abscesses: 7
Metabolic		
Dysmyelinating	Inflammatory (22): 23.65%	Chronic MS: 12
Mitochondrial		Acute MS: 4
Inherited		ADEM: 6
	ischemic (29): 31.18%	17: infarction (in different stages)
		12 hematoma (in different stages
	Metabolic (2): 2.15%	Wilson disease: 2
	Mitochondrial (4)::4.31%	Leigh disease 4
	Inherited (3): 3.22%	Metachromatic leukodystrophy(MLD): 3
Total no of patient	93 patients	

and mitochondrial with defective formation or maintenance of myelin (see Table 1) (1). MR spectroscopy has the potential for discriminating the presence and relative amount of various chemical metabolites in the brain and is therefore a useful technique to further assess various intracranial diseases, particularly to specifically determine which major category of disease is manifested by the observed lesion (e.g., neoplastic, inflammatory, ischemic (2)). The aim of our study was to assess metabolic changes by MRS of different white matter diseases diagnosed by MRI and evaluate peaks of inflammation.

2. Patients and methods

The study population included a total of 93 patients, 49 females and 44 males with age ranging from 2 to 63 years, with total number of 258 examined white matter hyperintense lesions on T2, FLAIR and/or contrast enhanced MRI sequences diagnosed on MRI lesions, 68 with single bilateral lesions and 25 with multiple bilateral lesions. This study was performed after the approval of the faculty ethical committee, and informed written consent was obtained from all patients or patient's parents. During a period from January 2014 to July 2015, 93 patients (44 males and 49 females), age ranging from 2 to 63 years (mean 37 ± 2.34) were included in this study. All had a focal white matter diseases recently diagnosed by MRI and had received no previous treatment, except for steroids. They were referred for MRS examination before starting treatment. All patients were subjected to history taking, clinical examination, MRI and MRS examinations and findings are correlated with laboratory, response to treatment received by the patient, and/or follow-up by MRI and MRS examinations with histopathology correlation if available.

The spectroscopic data were processed on a Philips 1.5 Tesla workstation (Gyroscan Entera, Philips medical systems) using standard imaging head coil. Images were acquired with the patient on supine position with a placed head support pillow to minimize the patient's movement. The procedure was explained carefully to the patients. They were asked to relax and stay still during the examination, and oral administration of chloralhydrate (50 mg/kg body weight) was given to sedate young patients during the exam. The volume of interest (VOI) was determined by T2 FLAIR and/or contrast enhanced axial T1-weighted images simultaneously to ensure that voxels were placed over the whole area of signal alteration, and the voxel was centered on the region previously noted including the bilateral basal ganglia, thalami, white matter, ventricles, brain stem substantia nigra cranial nerves and red nuclei, to correspond to area of maximal T2 or T2 FLAIR abnormality and mass effect or maximum contrast enhancement. The size of the voxel ranged from $1 \times 1 \times 1$ cm^3 to $2 \times 2 \times 2$ cm^3 according to the size of the lesion, and the time of the whole MRS examination using the single voxel technique ranged from 40 min.

Three TE acquisitions sequences (long, short and intermediate TEs) were done. SVS studies were performed with Point Resolve Spectroscopy sequence (PRESS).

MRS technique: First: Axial, sagittal and coronal planes of the brain were done in T2WI:TE = 100, TR = 3658, Field of view (FOV) 18 × 24 cm and Matrix 192 × 256.

Then, MRS in long TE = 288, short TE = 31 and intermediate TE = 144 with TR = 2000 and spectral bw = 1000. The long TE spectrum was to evaluate Cho, NAA, Cr and lipid lactate peak. The short TE spectrum was to evaluate myoinositol, glycine and glutamate, succinate and amino acid peaks.

The signal intensity of various metabolite peaks was evaluated in every voxel by using the integral of each peak as a measure of its intensity. Metabolite ratios for Cho/NAA, Cho/Cr, NAA/Cr ratio, and Glx, mI and peak were automatically calculated in each voxel of whole area of signal alteration including the contrast-enhancing area (when present). Succinate lac/Cr ratio and amino acid peak were studied in specific cases.

The statistical analysis of data was done using SPSS (Statistical Package for Social Science, version 16 Inc., Chicago, IL) program software package for windows. The mean and SD value of the metabolite ratios for different white matter lesions diagnosed by MRS was calculated.

3. Results

Cho/Cr and Cho/NAA ratios were lower and NAA/Cr ratio was higher compared to the expected ratios in neoplastic brain lesions (Table 2). Dominant metabolite for ischemic lesions, was the Lip/Lac that was also consistent in the ischemic lesions.

In demyelinating diseases, we had reliably increased myoinositol (MI) peaks, and the metabolic disease group showed raised glutamate (Glx) peak.

Table 2 Mean and standard deviation of main metabolite ratios in different white matter diseases.

White matter lesions	Cho/NAA	Cho/Cr	NAA/Cr
Infectious	0.79 ± 0.19	0.95 ± 0.17	1.89 ± 0.69
Inflammatory	0.65 ± 0.15	0.98 ± 0.29	1.69 ± 0.19
ischemic	0.83 ± 0.09	0.81 ± 0.23	1.54 ± 0.39
Mitochondrial	0.62 ± 0.19	0.54 ± 0.14	1.49 ± 0.59
Metabolic	0.57 ± 0.13	0.76 ± 0.26	1.73 ± 0.44
Inherited	0.51 ± 0.17	0.63 ± 0.13	1.87 ± 0.65

Cho resonances increase in acute MS plaques and tuberculous abscesses, and elevated Cho levels and reduced NAA levels had been reported in acute MS plaques.

Creatine (Cr) is considered to be an indicator of energy metabolism, generally decreased in chronic MS plaques, increased in acute MS and in glial tumors, Glx glutamate and myoinositol peak raised in inflammatory and infectious groups especially in the acute stage, Glx is high in all acute MS cases (Table 3), mildly raised in 2 out of 12 chronic MS and in 2 out of 6 cases of ADEM and reduced in 10 out of 12 chronic MS and 4 out of 6 of ADEM, Glx is high in all cases of TB, mildly raised in encephalitis, high in all acute and subacute and low in chronic ischemic cases.

In cases of ischemia, we had raised choline level in all cases of the acute and subacute stage and 7 out of 14 of chronic stage, increased MI in the acute and subacute stage, and MI is also high in acute MS, raised in TB, brain abscesses, encephalitis, and low in chronic ischemia and ADEM. Lac is produced in anaerobic glycolysis and is more prominent in ischemic diseases and acute infarction, Lac/Cr ratio in MLD ranges from 0.2 to 0.4.

Lip usually correlates with the extent of tissue short relaxation time seen in acute MS plaques and brain abscesses, and Lip–Lac metabolites routinely were undetectable in healthy brain.

Mitochondrial lesions (Leigh's disease) showed in average elevated choline, occasionally elevated lactate and reduced NAA.

Amino acids and succinate peak raised in all brain abscesses with mild increase in cysticercosis.

In metabolic group, MI and Glx were increased with lipid/lactate peak which is also noted.

4. Discussion

MRS contributed to correct diagnosis of encephalic lesions with diverse etiologies, such as infectious, ischemic, demyelinating, inflammatory, malformation of brain development and phacomatosis (3).

Table 3 Other metabolite changes in white matter diseases.

White matter lesions	Glx peak	MI peak	Succinate peak and amino acids	Lip/Lac ratio	Lac/Cr ratio
Infectious	+ + + in TB + in encephalitis	+in TB brain abscesses encephalitis	+ + + in brain abscesses + cysticercosis	+ + in TB, brain Abscesses, encephalitis − − − cysticercosis	− − − − −
Inflammatory	+ + + in acute MS + in chronic MS and ADEM − − − − in chronic MS and ADEM	+ + + in acute MS + in chronic MS − − − − in ADEM	− − − − −	+ in ADEM	− − − − −
Ischemic	+ + in acute and subacute − − − − − in chronic cases	+ + in acute and subacute − − − − − in chronic	− − − − −	+ + in acute and subacute + in chronic cases	− − − − −
Mitochondrial	+	+	− − − − −	+ +	− − − − −
Metabolic	+	+ +	− − − − −	+ +	− − − − −
Inherited	+ +	+ + +	− − − − −	+ +	+ +

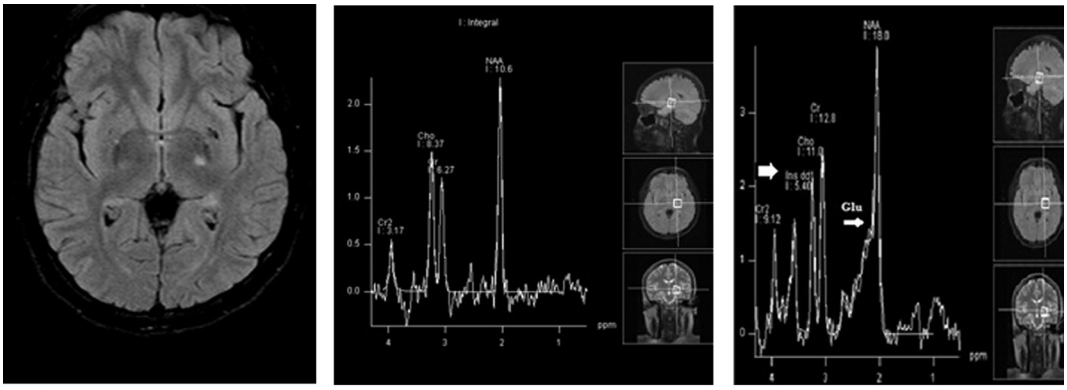

Fig. 1 Female patient 24 years old with acute MS (A) Axial MRI brain T2 weighted FLAIR images showed left basal ganglia hyperintense lesion, (B) and (C) MRS at long and short TR showed: Elevated glutamate (thin white arrow) and myoinositol (thick white arrow), with elevated cho/Cr.

NAA is a marker of functional neurons and decreases in all kinds of brain damages whether it is infiltrative, degenerative or destructive processes (4). Cho resonances increase in acute MS plaques and tuberculous abscesses due to increased cell membrane synthesis and turnover (5,6). Cr is considered to be an indicator of energy metabolism, generally increased in chronic MS plaques and decreased in acute MS (7–9). Lac is produced in anaerobic glycolysis and is more prominent in ischemic diseases and acute infarction, and Lip usually correlates with the extent of short relaxation time of tissue, generally seen in acute MS plaques and brain abscesses. Lip–Lac metabolites routinely were undetectable in healthy brain (10–12). Glx is a neurotransmitter, generally increased in Wilson disease; elevated Cho levels and reduced NAA levels had been reported in acute MS plaques and had been explained by reactive astrogliosis, inflammation and early axonal degeneration, and MI at short TE was also a discriminating metabolite for the acute MS and also increased in cases of glial activation or gliosis (13) in Multiple sclerosis: in acute lesions there is an elevation of glutamate in contrast-enhancing areas This is consistent with active inflammatory infiltrates (Fig. 1). It can be seen as a new in vivo marker of inflammation (14), they are also characterized by lac increase, depending on the degree of inflammatory reaction, increased Cho/Cre ratios are due to acute myelin breakdown, but usually not so intense as in neoplastic lesions, and follow-up MRS exams will show distinct patterns of metabolic changes in these two conditions (14).

An increase in creatine is also noted, and Choline was elevated, possibly due to an increase in cell turnover and/or myelin debris, as reported previously (15). NAA peaks may be reduced within plaques, which is the most common and remarkable finding, Cho and lactate are found to be increased in the acute phase (15), this is in agreement with our cases in the acute stage as elevation of glutamate and myoinositol peak, and CHO/Cr ratio is noted in all cases (100%) (Fig. 1). However, mild lac increase is noted in only one case out of 4 (25%).

In Inactive or 'chronic' multiple sclerosis plaques, glutamate levels were not different in non-enhancing chronic T1-hypointense areas. We believe this is due to the absence of activated immune cells in chronic plaques. However, NAA was significantly reduced in chronic T1-hypointense areas with elevation of myoinositol. Both of these findings are consistent with pathological evidence of reduced axonal density and gliosis (Fig. 2). Since NAA is consistently reduced in chronic lesions (16) it would be important to find predictors of this decrease in the early enhancing phase of lesions. Chronic plaques present reduced NAA/Cr ratios in the center of the

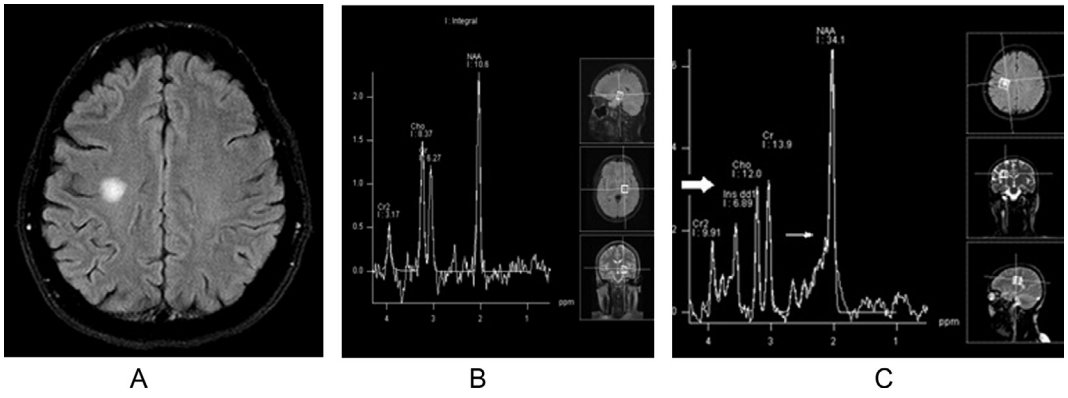

Fig. 2 Female patient 36 years old with chronic MS (A) Axial MRI brain T2 FLAIR images showed right parietal hyperintense lesion, (B) and (C) MRS at long and short TR showed: Reduced glutamate (thin white arrow), mild raised level of myoinositol (thick white arrow), and reduced NAA/Cr ratio.

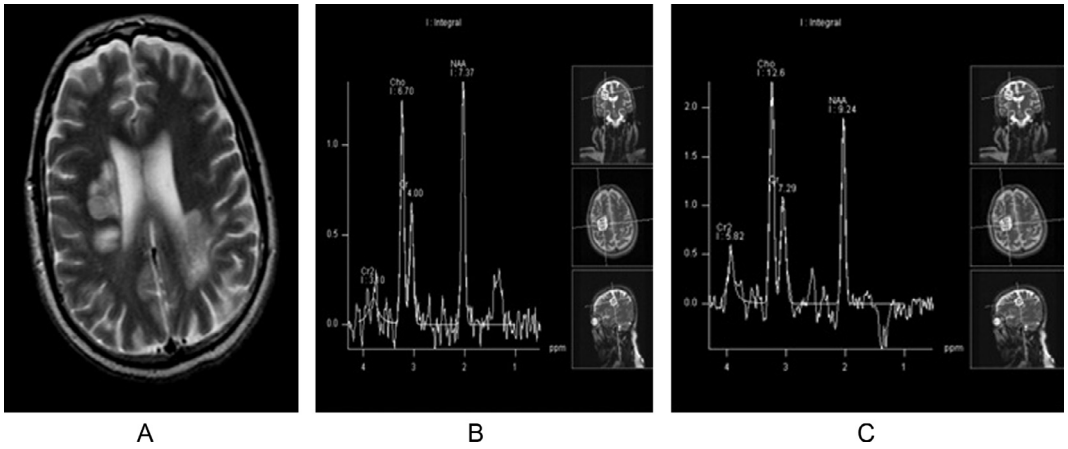

Fig. 3 Female patient 28 years old with acute disseminated encephalomyelitis phase (A) Axial MRI brain T2 weighted images showed bilateral periventricular hyperintense lesions, (B) and (C) MRS at long and short TR showed: High choline/Cr, raised lactate peak, with no MI detected.

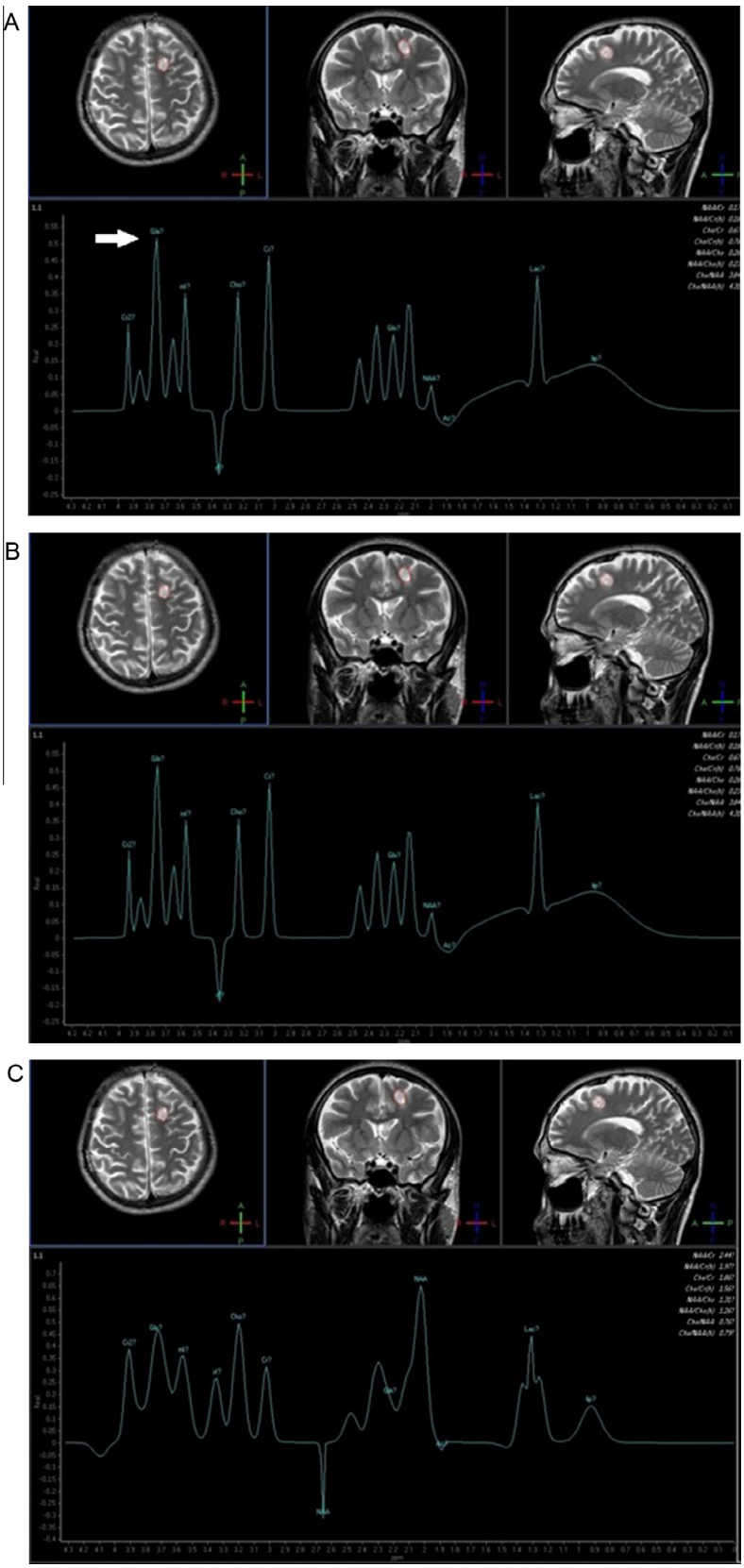

Fig. 4 Male patient 17 years old with brain TB (A, B & C) MRI axial T2 weighted image of the brain and MRS revealed: left frontal subcortical intraaxial focus of altered signal intensity: MRS at long and short TR revealed. Well observed Glx peak (white arrow) (Fig. 1A). Cho/Cr: 1.76, NAA/Cr: 0.98, MI/NAA: 0.567.

lesion, as consequence of irreversible axonal injury and partial or complete recovery of NAA signal in the periphery of the lesion. This is in agreement with our chronic cases as Naa/Cr ratios are reduced with mild elevation of MI in all cases with reduced Glx in 10 out of 12 (83.33%) and mild elevation in 2 out of 12 of chronic cases (16.66%) (Fig. 2).

In Acute disseminated encephalomyelitis (ADEM) Reduced NAA/Cr ratios were detected during both the acute and chronic phases while the Cho/Cr ratios were high during the acute phase and decreased toward normal values during the chronic phase (17). Major differences were found between the acute and chronic phases in the mI/Cr ratio and in the appearance of lipids and Glx. A marked reduction in mI/Cr ratio was detected during the acute phase (Fig. 3) followed by elevated values during the chronic phase in all patients. The higher level of mI during the chronic phase likely reflects a pathophysiological process of gliosis (18). These results are matching with our results as in the acute phase, and elevated lipids/lactate ratios were noted with marked reduction in the MI/Cr that was detected in all cases (Fig. 3). These peaks are normalized during the chronic phase. However Glx peak is reduced in 4 out of 6 cases (66.6%).

Tuberculous lesions have been shown to exhibit strong lipid resonances, ascribed to mobile lipids within the caseous material (19,20), which are minimally visible on MR imaging. The diagnosis of a granuloma was based on the presence of high lipid peak and Glutamine/Glutamate (Glx) peak (21,22). This is in agreement with our tuberculoma cases, all showed high (Glx) and lipid peak (Fig. 4).

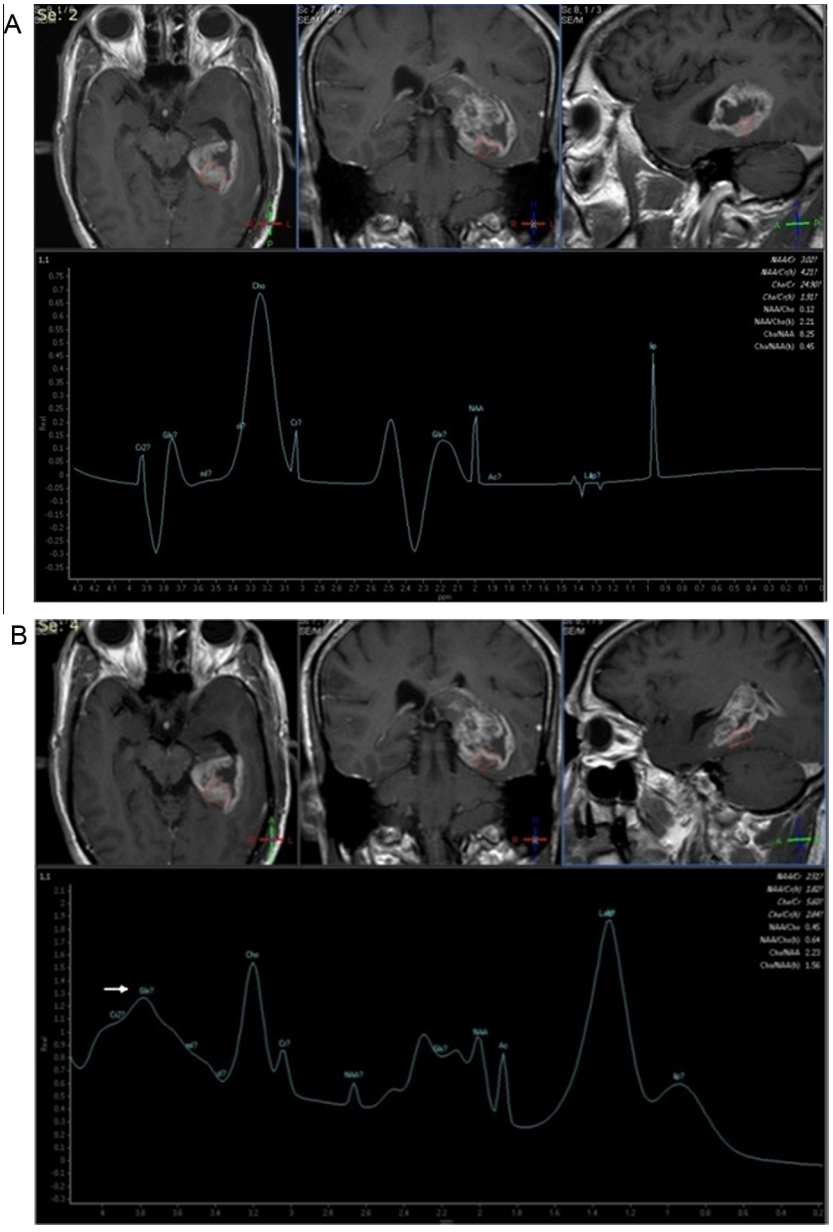

Fig. 5 Male patient 37 years old with encephalitis (A & B) MRI and MRS axial post-contrast T1 weighted showed left deep temporoparietal enhanced lesion, and MRS at long and short TR showed: Cho/Cr: 1.7, NAA/Cr. 2.11, Cho/NAA 0.47, prominent lip/lac peak. Mild prominent MI peak, glutamate peak is noted (thin white arrow).

Encephalitis is usually characterized by the following: ↓ NAA and NAA/Cr, this reduction may be more significant in the chronic phase of encephalitis, and there can be gradual recovery within 1 year. (23), ↓ Cr. ↑ Cho, Cho/Cr, marked increase in the Cho levels and Cho/Cr ratio can be seen in encephalitis, particularly secondary to herpes virus because of marked infiltration of macrophages. In this case, the spectral pattern may resemble that of a neoplasm. Associated increase in myoinositol (ml) should be suggestive of infection. ↑ ml, mI/Cr, this is a common finding in encephalitis and relates to gliosis. Lipid/lactate peak may be seen. ↑ Glutamate and glutamine demonstrated (24).

These results are coincoiding with our cases of encephalitis regarding the positive Glx and lipid/lactate peak and increased Cho/Cr ratio compared to the normal side in 100% of cases (Fig. 5).

Acetate, succinate and amino acid multiplet – composed of valine, leucine and isoleucine – are markers of bacterial abscess (25) and they are not detected in necrotic tumors such as metastasis and glioblastoma, which sometimes mimic brain abscess in conventional MR. Other types of abscess, such as tuberculous, do not show this pattern. In addition, the characteristic neural tissue peaks (NAA, Cho, Cre) are absent or decreased, confirming the brain tissue destruction in necrotic area (26), and these results are coincoiding with all our cases of brain abscesses that showed high succinate and amino acid peak with reduced Cho/NAA and Cho/Cr ratios (Fig. 6). Neurocysticercosis is the most common parasitic CNS infection across the world. When the acute lesion is single, parenchymatous, with reactive edema, it may simulate an encephalic tumor (27). However, succinate signal is elevated in neurocysticercosis and has been associated with the aerobic metabolism of scolices, Amino acid peaks have also been found in neurocysticercosis lesions (27), this is in agreement with our cases of cysticercosis all showed elevated succinate and mild raised A.A peak (Fig. 7).

Subacute infarction associated with lactate increase can be detected in minutes after the ischemia and continues increasing in the following hours (28,29). Choline might be elevated in acute infarcts because of the high cellular turnover. Subacute infarctions show decreased NAA (as a response to neuronal loss and dysfunction) and increased lac, with progressive Cho reduction in the chronic phase (30). High levels of glutamate in plasma and cerebrospinal fluid (CSF) have been demonstrated in patients with acute ischemic stroke (31).

Subacute infarction could be from differentiated neoplasm as follows: Increased lactate levels associated with reduced NAA, Cr, and Cho levels. However, it is important to

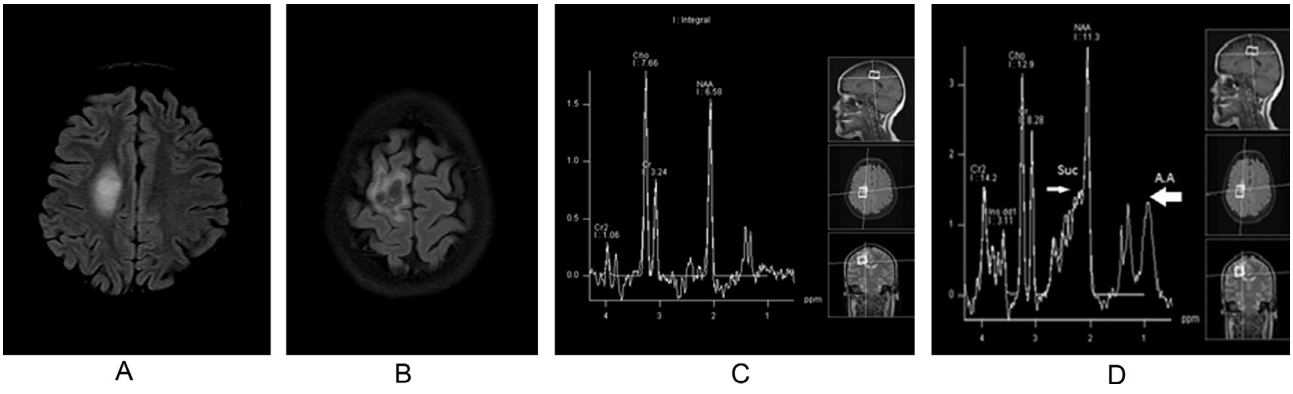

Fig. 6 Female patient 24 years old with brain abscess: (A & B) axial T2 and post-contrast T1 weighted images: revealed right parietal hyperintense lesion with thin marginal enhancement in post-contrast study, (C & D) MRS at long and short TR revealed: raised A.A peak at 0.9 ppm (thick whited arrow), succinate peak at 2.4 ppm (thin white arrow), raised lipid/lactate peak and reduced Cho/NAA and Cho/Cr ratios.

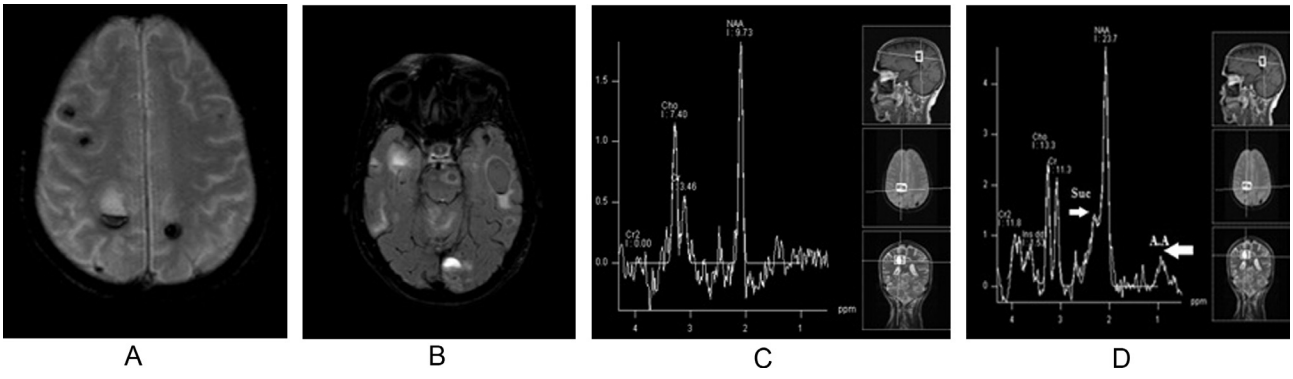

Fig. 7 Female patient 33 years old with brain cysticercosis, (A and B) axial T2 weighted and post-contrast T1 WI images of the brain, revealed multiple widespread calcified intra-axial lesions hyper and hypointense on T2 WI and marginal contrast enhancement. (C) and (D) MRS at long and short TR revealed: There is reduction in the creatine due to high metabolic rate, Cho/NAA: 0.76, Cho/Cr: 1.3, NAA/Cr: 1.53, A.A is mild elevated (thick white arrow), and succinate peak at 2.4 ppm (thin white arrow).

remember that increased Cho levels may be observed in infarctions especially in the chronic stages because of remyelination and gliosis, and they should not be mistaken for a neoplasm. This is in agreement with our study in all cases of subacute infarct, regarding elevated lipid/lactate peak raised (Glx) peak in the acute and subacute stage (Fig. 8) and its decrease in the chronic stage (100%); however, we disagreed regarding low choline level in chronic stage, as we had high level in chronic stage in 7 out of 14 cases (50%) denoting remyelination and gliosis.

Wilson disease (hepatolenticular degeneration) is an autosomal recessive disorder of copper metabolism. Glx is a neurotransmitter, generally increased in Wilson disease (32), which coincoides and agrees with our results.

In MLD, there is elevated myoinositol/creatine and lactate/creatine ratios as well as decreased N-acetyl aspartate/creatine ratios. The mean of the Lac/Cr ratios in MLD cases was 0.42 compared to 0.11 in the control subjects. Elevated lac/Cr and mI/Cr are both attributable to astrocytic gliosis ch/ch of MLD elevation (33). Myoinositol and lactate may be used as biomarkers for disease progression in MLD. We also noted a slight elevation in the Cho/Cr, Inverted lactate doublet peak-increased choline peak and decreased NAA\Crea ratios with conjunction to the pathognomonic brain MRI findings and elevation of lactate in CSF, is enough to diagnose the disease (33); the results are matching with all our cases MLD, they showed high myoinositol (MI) level, raised lipid/lactate, MI/Cr ratio, lac/Cr higher than 0.2 in all cases (Fig. 9).

Leigh's disease one of many mitochondrial disorder also known as subacute necrotizing encephalomyelopathy (SNEM) symptoms becomes evident before the age of 2, with high T2 signal typically in brainstem, periaqueductal gray matter, medulla, putamen, corpus striatum, globus pallidus, caudate nuclei, substantia nigra, thalami, MR spectroscopy features of elevated choline, occasionally elevated lactate, and reduced NAA (34), this is in agreement with all our cases of Leigh's disease that showed elevated lipid/lactate peak, elevated Cho\-crea ratio with reduced NAA\Cr ratio (Fig. 10).

Excess glutamate in active lesions could therefore be an important predictor of axonal injury, brain atrophy and long-term accumulation of clinical disability (35). In infectious disease the presence of Glx and MI peak with high lipid/lactate supported the diagnosis. Succinate and amino acids are specific for brain abscesses and cysticercosis. Other categories were

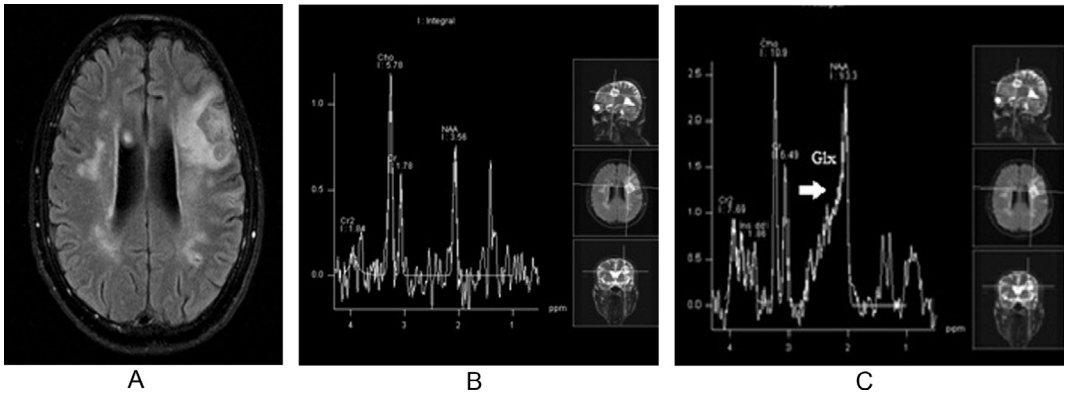

Fig. 8 Male patient 57 years old with subacute hemorrhagic infarction presented with right sided weakness: findings: (A) axial T2 FLAIR images revealed left cortical and subcortical high signal intensity lesion with multiply intralesional areas of altered signal intensity, (B & C) MRS at long and short TR revealed elevated Cho, reduced NAA/Cr with high Glx (thick white arrow) and lipid lactate peak.

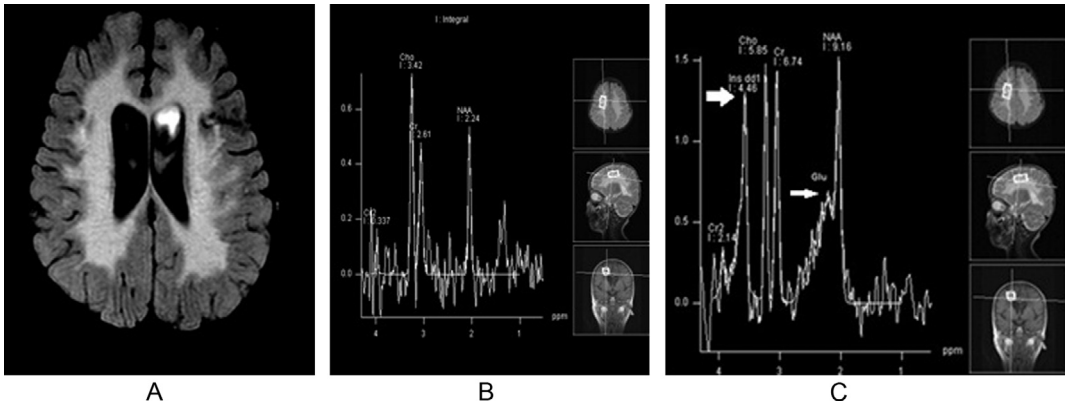

Fig. 9 Child male 3 years old with metachromatic leukodystrophy (A): axial T2 FLAIR images of the brain revealed bilateral symmetrical confluent areas of signal change in periventricular white matter with characteristic tigroid appearance, (B & C) MRS at long and short TR shows high myoinositol (mI) level (thick white arrow) and Glx (thin white arrow) (C), raised lipid/lactate with high MI/Cr level, lac/Cr 0.32.

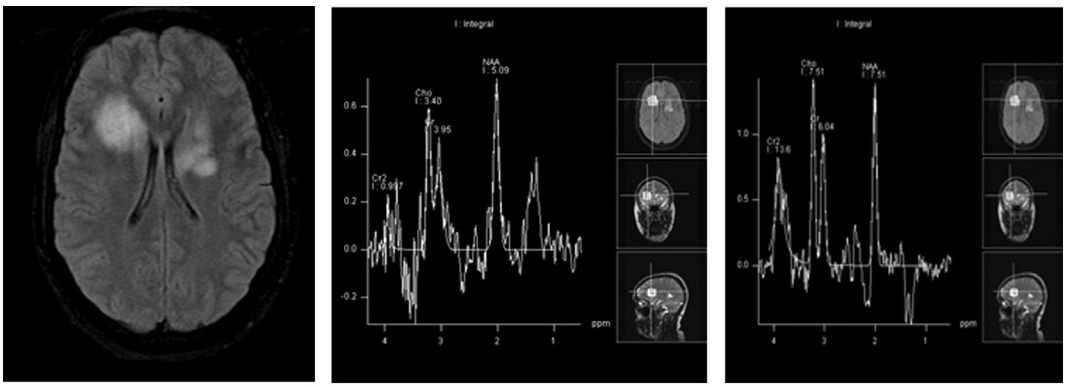

Fig. 10 Child female patient 3 years old with leigh's disease: (A) MRI axial T2 FLAIR of the brain revealed bilateral deep white matter hyperintense lesion, (B & C) MRS at long and short TR showed: Elevated lipid/lactate peak, elevated Cho/crea ratio. NAA/Cr ratio was decreased.

differentiated by the pattern of ratios among NAA, Cre, Cho and lac in conjunction with other imaging findings.

The limitation of our study is that single voxel MRS value is limited in both resolution and anatomical coverage of white matter lesions.

5. Conclusion

Proton MRS is a noninvasive additional MRI technique to define the nature of non-neoplastic brain lesions. Together with image analysis, it may be the key to etiologic diagnosis or, at least, definition of the group where the lesion is classified, by detecting changes in different metabolites and peaks of inflammation.

Conflict of interest

No conflict of interest.

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