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Original Article

Magnetic Resonance Spectroscopy Role in Assessment of Pediatric Supratentorial Brain Lesions

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ABSTRACT

Background: Magnetic resonance spectroscopy [MRS] is of value for pediatric neurologist, as it confers relevant information from the clinical point of view. It is worth for brain tumors, infections and disorders of the white matter. MRS metabolites add additional value to the therapeutic solutions when MRS combined with other high-resolution imaging modalities.

Objective: The current work aimed to assess the role of magnetic resonance spectroscopy in pediatric supratentorial brain lesions.

Patients and methods: This study recruited a convenient sample of thirty patients [21 females and 9 males]. Their age ranged between one and sixteen years. All were submitted to single-voxel H-MR spectroscopy with the same MR unit using point resolved spectroscopy [PRESS] sequence, using short TE [35] and long TE [144] spectra. Then spectrum analysis was performed to obtain the important ratios: choline/N-acetylaspartate, choline/creatine and mI/Cr to reach the diagnosis of the supratentorial lesion.

Result: The choline/N-acetylaspartate [Cho/NAA], choline/creatine [Cho/Cr] and mI/Cr ratios were statistically difference between neoplastic and non-neoplastic lesions at cutoffs 2, 1.6, & 1.15 respectively. The peak of lipid lactate was only present and significant for differentiating high- from low-grade tumors.

Conclusion: MRS is valuable in differential diagnosis of brain lesions, as it differentiates neoplastic from non-neoplastic tumors. It also plays a complementary role with magnetic resonance imaging [MRI] in the follow up of therapeutic response.

Keywords: Brain; Tumors; Pediatric; Magnetic Resonance Spectroscopy; Metabolic Ratios

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INTRODUCTION

The ability to differentiate between neoplastic and non-neoplastic brain lesions is often a challenge for the clinician and neurosurgeon. The conventional imaging techniques cannot always provide detailed information about the nature of the lesion [1]. The histopathology is the gold-standard for defining the neoplastic nature of the lesion. Thus, many patients submitted to invasive techniques [2]. Magnetic resonance imaging [MRI] is a non-invasive imaging modality for the diagnosis, staging, and follow up after treatment of the pediatric brain lesions. It was considered the corner-stone for the diagnosis of brain tumors in many cases. However, confident differentiation of neoplastic from non- neoplastic brain lesions or low from high-grade tumors is problematic with conventional MRI [3].

MR spectroscopy [MRS] can evaluate neurological disorders in pediatric age group at the microscopic level by analyzing different cellular metabolites and assessing their tissue distribution. The commonest available MRS modality is the proton [1H; hydrogen] spectroscopy [4]. There is a wide list of metabolites that may be useful in the MRS evaluation of brain lesions including: NNA [N-acetyl-aspartate], choline, creatine, lipids, lactate, alanine and myo-inositol [5]. MRS helps to afford more clinically relevant data for several neurological diseases of pediatrics [e.g., brain neoplasms, infectious conditions and white matter disorders] [6]. When used in combination with the high-resolution anatomical imaging modalities [e.g., conventional MRI], MRS metabolites can improve neuro-pathological diagnostic data and improve the therapeutic decisions [7].

Conventional computed tomography [CT] and magnetic resonance imaging [MRI] cannot differentiate between neoplastic and non-neoplastic conditions in a reliable way. This warrant further investigates to reach the final diagnosis. One of the unique imaging modalities is the magnetic resonance spectroscopy [MRS], which could differentiate between neoplastic and non-neoplastic brain lesions. This could be achieved by the measurement of chemical composition of the brain tissues. Using different chemical variables and ratios, a reliable etiology of a particular condition could be reached using non-invasive, painless procedures [8].

The non-invasive accurate diagnosis and differentiating tumorous from non-tumorous brain lesions of the children, as well as differentiating the low from the high-grade tumors is crucial in the construction of the correct treatment plan. MRS provides valuable data about biochemical characteristics, metabolic composition of the lesions and the surrounding structures [3]. Proton [^{1}H-MRS] can guide the clinical decision-making in pediatric neuro-oncology, by the introduction of the valuable information, not obtained by the conventional imaging. This permits timely counseling, proper diagnosis and early intervention [9].

THE AIM OF THE WORK

The current study was designed to evaluate the role of magnetic resonance spectroscopy [MRS] in pediatric supratentorial brain lesions.

PATIENTS AND METHODS

This study was performed between July 2021 and March 2022. It was completed at the department of Radiology, Al-Azhar University Hospital [New Damietta]. It included 30 patients [9 males and 21 females]. Their ages ranged between one and 16 years. Patients were referred from the Neurosurgery and Neurology departments. In addition, they were also referred from the outpatient clinics on the basis of the need for specific and accurate diagnosis of the doubtful brain lesion.

Inclusion criteria were children below 16 years of age, who had diagnosis of brain lesions, and of both genders. On the other side, exclusion criteria were any contra-indications to the use of MRI examination or the contrast agents [e.g., metallic prosthesis or artificial pacemakers], uncooperative or patients with claustrophobia, patients who had behavioral or mental disorders, patients with severe allergy or renal impairment

Ethical considerations: The study was approved by the local ethics committee of our institute, and informed consent was obtained from all participants prior to initiation of the study. All patients were submitted to complete history taking, review of all previous radiological examination, clinical examination [completed by the referring physician], and laboratory investigations [e.g., serum creatinine]. In addition, all patients were submitted to brain imaging using Philips Medical Systems [Achieva 1.5 Tesla scanner -XR- Best, Netherlands 2010] with a standard head coil.

The Conventional MRI were performed in axial and sagittal T1-weighted pre-contrast spin echo. Then, axial FLAIR, axial and coronal T2-weighted fast spin-echo images were obtained. Furthermore, the contrast-enhanced axial, sagittal and coronal T1-weighted spin-echo images were obtained by the Gad-DTPA [Magnevist or Omniscan] 0.1 mmol/kg.

The MRS were performed for all patients. The single-voxel ^{1}H-MRS was carried out by the same MR unit using the sequence of the point resolved spectroscopy [PRESS]. A volume of interest [VOI] between [1 and 8 cm^{3}] was placed. Its size and location were evaluated by the largest possible voxel positioning within the brain lesion [mainly the enhancing part], with minimal contamination from the surrounding tissue. Two spectra were obtained from the same VOI for every patient at: 1] the short TE [2000/31] [TR/TE]; and 2] the long TE [2000/144]. The spectrum analysis was done offline with the use of the software integrated within the Achieva 1.5 Tesla scanner [spectro-option]. The data points intensities of the spectrum between 0 and 4.00 ppm were selected and used as input for the normalization and analysis. The frequency domain chemical shifts were internally referenced to creatine [Cr] 3.03 ppm and/or 11C-choline [Cho] 3.22 ppm.

Different metabolites were selected. For example, in the long TE, the metabolites were choline [at 3.2ppm], N-acetylaspartate [at 2.0ppm], creatine [3.02ppm]. However, in the short TE, the metabolites were MI [at 3.56ppm] as well as lipid/lactate peaks [between 1 and 1.5 ppm], alanine [between 1.3-1.4ppm], and glutamine and glutamate [Glx] [between 2 and 2.5pm]. In addition, important ratios were calculated. The integral and intensity values were calculated for each metabolite. Then, the intensity value was used to obtain the important ratios that were essential to reach the diagnosis. Cho/NAA, Cho/Cr and mI/Cr ratios within the lesion were calculated. According to the results of radiological evaluation, a preliminary differentiation of the lesions into tumors or non-tumors was carried out and documented.

Statistical analysis was performed by the statistical package for social sciences [SPSS] version 25 [IBM®SPSS, Inc. Chicago, USA]. Mean and standard deviations were calculated for numerical values, while relative frequency and percentages were calculated for categorical variables. The association between the metabolite ratios and the final diagnosis was assessed by the Receiver Operation Characteristic [ROC] curve. The area under the curve [AUC] was used to estimate the optimal cutoff points for differentiation.

RESULTS

Thirty patients were included in this study, their age range [1 to 16 years; mean age 8.59]. They were 9 males [30 %] and 21 women [70%]. Thirty high-quality MRI and MRS examinations were available for the study. These examinations were classified into two groups: neoplastic and non-neoplastic. Nine out of the 30 patients [30.0%] had intracranial tumors. They were submitted to stereotactic biopsy or surgery and final histopathological diagnosis was obtained. The remaining 21 cases had non-neoplastic lesions according to the clinical and radiological follow-up results. Significant difference was found at 3.55-ppm Myo-Inositol [MI] at short TE. There were significantly higher values in neoplastic tumors. However, at long TE, N-acetylaspartate at 2.02-ppm was higher in non-neoplastic lesions, and at 3.22-ppm choline, there was higher values in neoplastic lesions. Furthermore, at 3.03 ppm creatine was significantly higher in non-neoplastic lesions.

Ratios between resonances at each TE were defined to create a variable that was used as reference in classification between the two groups [i.e. tumors & non-tumors]. Two possible ratios were considered at the long TE [Cho/ NAA and Cho/Cr]. At the short TE, as only MI showed significantly higher values in some tumors. The mI/Cr ratio was selected for the short TE spectra. ROC curves were constructed, and at the long TE spectra, for Cho/ NAA, area under curve [AUC] was 0.921; for Cho/Cr, the AUC was 0.876 and at the short TE spectra, mI/Cr AUC was 0.992 [Table 1]. We selected the cutoff values of the curve that provided the best relationship between sensitivity and specificity at the long TE, and the short TE, to differentiate neoplastic from non-neoplastic tumors. They were:

- Cho/NAA ratio of ≥ 2 at long TE [sensitivity, 89%; specificity, 81%].
- Cho/Cr ratio of ≥ 1.6 at long TE [sensitivity, 89%; specificity, 81%].
- mI/Cr ratio of ≥ 1.15 at short TE [sensitivity, 100%; specificity, 95%].

Table [1]: ROC curve analysis results for metabolite ratios in neoplastic versus non-neoplastic differentiation of intracranial lesions, the diagnosis of tumor is selected when the ratio reaches the cut off value

	AUC	Cut off value	Sensetivity (%)	Specificity (%)
Cho/NAA	0.921	≥2	89 %	81 %
Cho/Cr	0.876	≥1.6	89 %	81 %
mI/Cr	0.992	≥1.15	100 %	95 %

Table [2]: The variety of the studied lesions

Diagnosis	Frequency	Percent
Craniopharyngioma	**7**	**23.33 %**
Central Neurocytoma	**1**	**3.33 %**
Low grade glioma	**1**	**3.33 %**
Hypoxic Ischemic leukoencephalopathy	**15**	**50.0 %**
Focal basal ganglionic ischemic lesion	**1**	**3.33 %**
Leukodystrophy	**1**	**3.33 %**
Encephalitis	**2**	**6.66 %**
Phakomatosis	**2**	**6.66 %**
Total	**30**	**100 %**

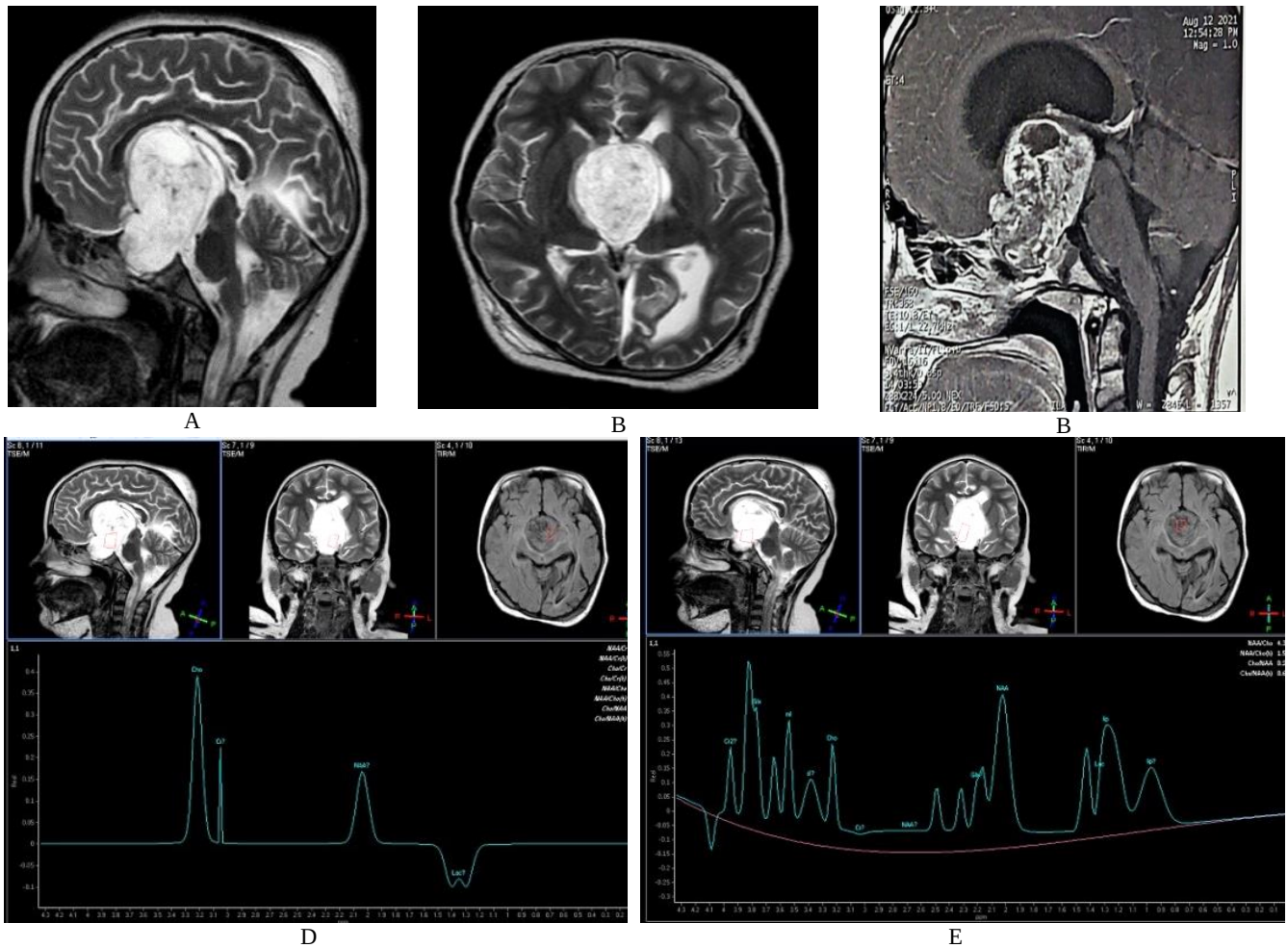

Figure [3]: A case of sellar & suprasellar craniopharyngioma of female patient 10 years old, presented clinically by headache, blurring of vision, and papilledema. **A, B** sagittal & axial T2 WIs show heterogeneous hyperintense sellar and suprasellar mass lesion, with mixed solid and cystic texture. Effacing supra-sellar cistern and indenting optic chiasma, and compressing of third ventricle. **C** sagittal T1 post contrast WI which show heterogeneous contrast enhancement. **D** PRESS long time echo spectrum [TE] 144 ms show decreased NAA, elevated Cho and inverted lactate peak, Cho/NAA ratio is 2.32 & Cho/Cr is 1.75. **E** short TE 35 ms show elevated lipids/macromolecules at 0.9 ppm, prominent lactate at 1.33 ppm, prominent mI peak at 3.55 ppm, mI/Cr ratio is 1.43. Histopathologically proved craniopharyngioma

DISCUSSION

In the current work, 1H-MRS improved the ability of radiologists to discriminate neoplastic from non-neoplastic brain lesions. We used a practically applicable method in differentiating tumors from their mimics by the evaluation of metabolite ratios at two different TEs [short and long]. Results suggested the diagnosis of the neoplastic lesions when Cho/NAA at long TE is ≥ 2

[sensitivity, 89 %; specificity, 81%], and Cho/Cr ratio at long TE is ≥ 1.6 [sensitivity, 89%; specificity, 81%]. At short TE, mI/Cr ratio of 1.15 was tested as a cut value for diagnosing tumor with sensitivity [100%] and specificity [95%]. Attia *et al*. [3] reported an increase of choline and reduction of NAA at the long TE. This suggested that a larger loss of neuron function and larger membrane turnover characterizes the neoplastic than non-neoplastic processes. They reported the diagnosis of neoplasm when Cho/NAA ratio was more than 2 at long TE [sensitivity, 88%; specificity 75%]. These data are supported by the current results. In addition, MRS is helpful to reach correct diagnosis of encephalic lesions of different etiologies [e.g., infectious, ischemic, demyelinating, inflammatory, malformations and phacomatosis] [10].

Myo-inositol is an important metabolite on MRS at the short TE. It is included in the process of proteolytic enzymes production, a character of aggressive primary neoplasms [11].

The current work found the resonance of lipids/lactate [LL] was elevated at 1.3-1.5 ppm, at higher grade gliomas. The lactate duplet was also noted in ischemic infarcts. This in line with previous work stated that, lactate is only found in pathologic states and acute stroke due to anaerobic glycolysis performed by the brain in ischemia or due to macrophage activation after membrane break down, as macrophages uses lactate for their energy supply [12]. Karatag *et al*. [13] evaluated the peak of LL in all cases and used it if present with Cho/Cr > 2.2 to differentiate high-from low grade neoplastic lesions with a sensitivity of 100% [82.2-100] and a specificity of 100%

Kaddah *et al*. [14] demonstrated that, the characteristic metabolite change of encephalitis was significant reduction of NAA and NAA/Cr ratio. This reduction was significant in the chronic phase of the disease, and gradual recovery was observed within 1 year. In addition, there was a reduction of creatinine, increase of choline and choline/creatine ratio. This was marked in encephalitis secondary to viral infection by herpes due to marked macrophages infiltration. Associated increase in myoinositol [ml] is suggestive of infection. Furthermore, there was a significant increase of mI, mI/Cr, due to gliosis. An increase in the lipid/lactate peak had been reported.

We reported a case of primary leukodystrophy. The MRS profile showed a highly elevated NNA peak, increased NAA/Cho ratio [about 5.27] and mild elevation of mI peak.

Sometimes, MRS failed to give helpful diagnostic data. This was observed for two cases of phakomatosis [Hyopmelanosis of Ito], where MRS metabolite peaks appeared normal, with slight prominent lactate peak. Comparing cranial neoplasms to all other non-neoplastic lesions, Cho/Cr and Cho/NAA ratios were higher in brain masses than the other non-neoplastic lesions. At the same time, NAA/Cr ratio was lower in brain neoplasms, and higher in non-neoplastic group.

The value of MRS in brain lesions, regardless its site, was confirmed in the study carried out by Tamilchelvan *et al.* [15] who examined the added value of advanced MRI and MRS for space-occupying lesions of the posterior cranial fossa. They included 40 patients [17 females and 13 males; the mean age was 34.67 years], and concluded that, conventional MRI was able to reach a diagnosis for the majority of the apparently benign lesions. However, the concomitant use of advanced MRI sequence [e.g., diffusion-weighted] or MRS helps in differentiation and proper diagnosis of these lesions closer to the diagnosis by the gold-standard histopathological examination.

In line with the current study, the diagnostic accuracy of MRS and its ability to differentiate neoplastic from non-neoplastic lesions of the brain had been investigated in the study performed by Alshammari *et al.* [1], who included 30 patients [14 males and 16 females; the mean age 44±18 years]. They reported higher ratios of Cho/Cr and Cho/NAA in astrocytoma, gliomas and meningioma when compared to non-neoplastic lesions. There was a good statistical agreement between histopathological results and that of MRS. In addition; MRS provided a diagnostic accuracy of 100%, and 82.60% sensitivity, 85.71% specificity, 95% positive predictive value and 60% negative predictive value. They concluded that, MRS is able to differentiate neoplastic from non-neoplastic brain tumors. Higher values of Choline-to- N-acetyl aspartate and choline-to- creatine ratios help clinicians and neurosurgeons in preoperative differentiating benign from malignant lesions.

We used to use single voxel technique to perform all MR spectroscopic examinations. This technique can be considered a limitation, as multivoxel methods can offer smaller VOIs and a better evaluation of tumor heterogeneity & compare the lesion with healthy contra-lateral side. However, single voxel techniques have some advantages, being quicker [so avoiding noisy signals from patient motion], providing the chance to obtain spectra at two different TEs in average amount of time which improves the level of accuracy.

Another limitation of the current work was the small number of cases, with evitable lower varieties of lesions and brain section limitation due to inclusion of the supratentorial sections. Future studies are recommended with inclusion of many patients to obtain a wide variety of brain lesions [both non-neoplastic & neoplastic].

Conclusion: MRS is a valuable imaging modality to differentiate neoplastic from non-neoplastic lesions of the brain in pediatrics. It also plays a complementary role with magnetic resonance imaging [MRI] in the follow-up of therapeutic response,

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