The Egyptian Journal of Radiology and Nuclear Medicine (2014) **45**, 211–217

Egyptian Society of Radiology and Nuclear Medicine

The Egyptian Journal of Radiology and Nuclear Medicine

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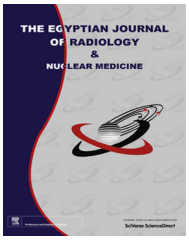

ORIGINAL ARTICLE

Predicting grade of cerebral gliomas using Myo-inositol/Creatine ratio

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Received 21 May 2013; accepted 8 July 2013
Available online 12 August 2013

KEYWORDS

Glioma;
Grading;
MRS;
MI/Cr

Abstract *Purpose:* Our aim was to determine the diagnostic accuracy of MI/Cr ratio in determining the grade of glioma.
Materials and methods: Twenty-two patients (14 males and 8 females), ranging in age from 15–63 years (mean 34.4 years) were prospectively recruited for this study. All had a brain tumor recently diagnosed by MRI and had received no previous treatment, except for steroids. They were referred for MRS examination before surgical biopsy and/or resection or radiotherapy. Ratios for MI/Cr, Cho/Cr, and Cho/NAA were obtained for each lesion and compared with the grade of the lesion.
Results: The levels of MI/Cr were higher (2.14 ± 1.4) in patients with low-grade astrocytoma, and lower in patients with anaplastic astrocytoma (0.39 ± 0.11) and GBM (0.025 ± 0.06). 21 out of the 22 patients were correctly classified using MI/Cr ratio, one patient was misdiagnosed as high grade glioma and the biopsy revealed grade II glioma. The diagnostic accuracy, sensitivity and specificity of MI/Cr ratio for the grading of glioma was 95.4%, 100%, and 92.8%, respectively.
Conclusion: MRS has proven to be an important complementary tool saving the patient from unnecessary biopsy taking when it is conclusive thus altering the treatment planning. This study had demonstrated that MI level and MI/Cr ratio are important in presurgical grading of brain tumors.

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Peer review under responsibility of Egyptian Society of Radiology and Nuclear Medicine.

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1. Introduction

Cerebral glioma is the most common type of primary brain tumor, and the prognosis for this disease remains very poor. Therefore, appropriate therapeutic measures are crucial for improving the prognosis of this devastating disease. In determining a treatment plan, tumor grade is a key consideration for minimizing the risk of unnecessary morbidity and mortality (1).

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According to the most recent revision of WHO classification system dated 2007, brain glial tumors can be classified into low grade (grade I and II, benign) and high grade (grade III and IV) (2).

The current "gold standard" for the determination of glioma grade is by surgical biopsy/resection and histopathologic assessment. However, biopsy approach may suffer from several sources of errors (3,4), the most significant of which is limited number of samples thus creating potential errors in determining glioma grade. As a result, a high-grade tumor may be diagnosed as low grade because the samples were taken at a less malignant region. Alternatively, noninvasive or minimally invasive imaging technologies have been used to evaluate the malignancy of brain tumors (1).

Because glial tumors have some specific metabolic characteristics which further differ according to the grade, there is growing interest in MR spectroscopy that could further increase the sensitivity of routinely used diagnostic imaging (5).

Recent reports regarding MR spectroscopy support its use as a powerful tool in tumor grading. Specifically, elevation in choline (Cho) with depression of N-acetylaspartate (NAA) is a reliable indicator of tumor (6).

Myo-inositol (MI) is one of the most abundant metabolites visible on 1H-MRS at short TE (30 ms). It can be detected as a multiplet of peaks with main components located at 3.5 ppm of the spectrum (5).

The concentration of MI is significantly increased in various cerebral diseases (7,8), including brain tumor (9). MI is involved in the activation of protein C kinase. Protein C kinase leads to the production of protylotic enzymes, which are found more often in malignant and aggressive primary tumors. Thus the level of MI as seen by MRS may be helpful for predicting the histologic grade of brain tumors (9).

The aim of this study was to determine the diagnostic value of MI/Cr ratio in determining the grade of cerebral glioma with reference to operative and histopathological results whenever possible.

2. Patients and methods

2.1. Patients

During a period from September 2011 to January 2013, 22 patients (14 males and 8 females), ranging in age from 15–63 years (mean 34.4 years) were prospectively recruited for this study. All had a brain tumor recently diagnosed by MRI and had received no previous treatment, except for steroids. They were referred for MRS examination before surgical biopsy and/or resection or radiotherapy.

This study was performed after the approval of the scientific and ethics committee of the hospital.

2.2. Methods

The study was performed on 1.5-T MR scanner (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.

Initially, each patient was subjected to routine spin echo (SE) sequences. The volume of interest (VOI) from the lesion was selected on SE-T2-weighted images for single voxel (SVS). The voxel was centered on the region previously noted to correspond to maximum contrast enhancement. If contrast enhancement was subtle or not present, the area of maximal T2 abnormality and mass effect was sampled.

The size of the voxel ranged from $1 \times 1 \times 1$ cm to $2 \times 2 \times 2$ cm according to the size of the lesion. The former used size of the voxel lead to a more lengthy examination compared to the latter one. So, the time of the whole MRS examination using the single voxel technique ranged from 40 to 50 min.

The three TE sequences (long, short and intermediate TEs) were done. SVS studies were performed with Point Resolved Spectroscopy (PRESS) sequence. Multi-voxel study was performed for one patient.

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.

3. Interpretation

Visually the important metabolites to be commented upon are;

- In the **long TE** were: the Cho (at 3.2 ppm), NAA (at 2.0 ppm), Cr (3.02 ppm) and sometimes the MI (at 3.56 ppm) as well as lipid/lactate peaks (between 1 and 1.5 ppm), however, it is better to comment on them in the short one.
- Other metabolites seen in the **short TE**, are MI and lipid/lactate (between 1 and 1.5 ppm).
- The **intermediate TE** was done to detect if there is inversion of the lipid/lactate peak or not, where if seen inverted denotes lactate. Presence of lipids denotes necrosis while lactate denotes high grade neoplasm (in neoplastic lesions)
- **Important ratios**

The intensity and integral values were obtained on each metabolite, and then we used the intensity value for obtaining the important ratios which were essential for reaching the diagnosis. Ratios for MI/Cr, Cho/Cr, and Cho/NAA were obtained for each lesion and compared with the histologic grade of the lesion.

The accuracy, sensitivity, and specificity were calculated for the correct identification of high grade gliomas. Hence, gliomas classified as high grade and found at histological examination to be of high grade were considered true-positive findings; low grade gliomas that were histologically confirmed as low grade were considered true negative.

4. Results

The tumor grades determined using MRS were compared with those obtained at histopathology/follow up by conventional MRI after radiotherapy. Sixteen cases were confirmed histologically via either surgical biopsy and/or resections, with 6 cases treated by radiotherapy. Follow up by conventional MRI was done in all cases.

According to the classification of WHO criteria, 14 patients with tumors were classified as low-grade gliomas, including WHO grade II (astrocystome ($n = 13$), oligodendroglioma ($n = 1$)), whereas in 8 patients the tumors were classified as high-grade gliomas, including 2 with WHO grade III (anaplastic astrocytoma) and 6 with WHO grade IV (glioblastomas).

The levels of MI/Cr were higher (2 ± 1.5) in patients with low-grade astrocytoma, and lower in patients with anaplastic

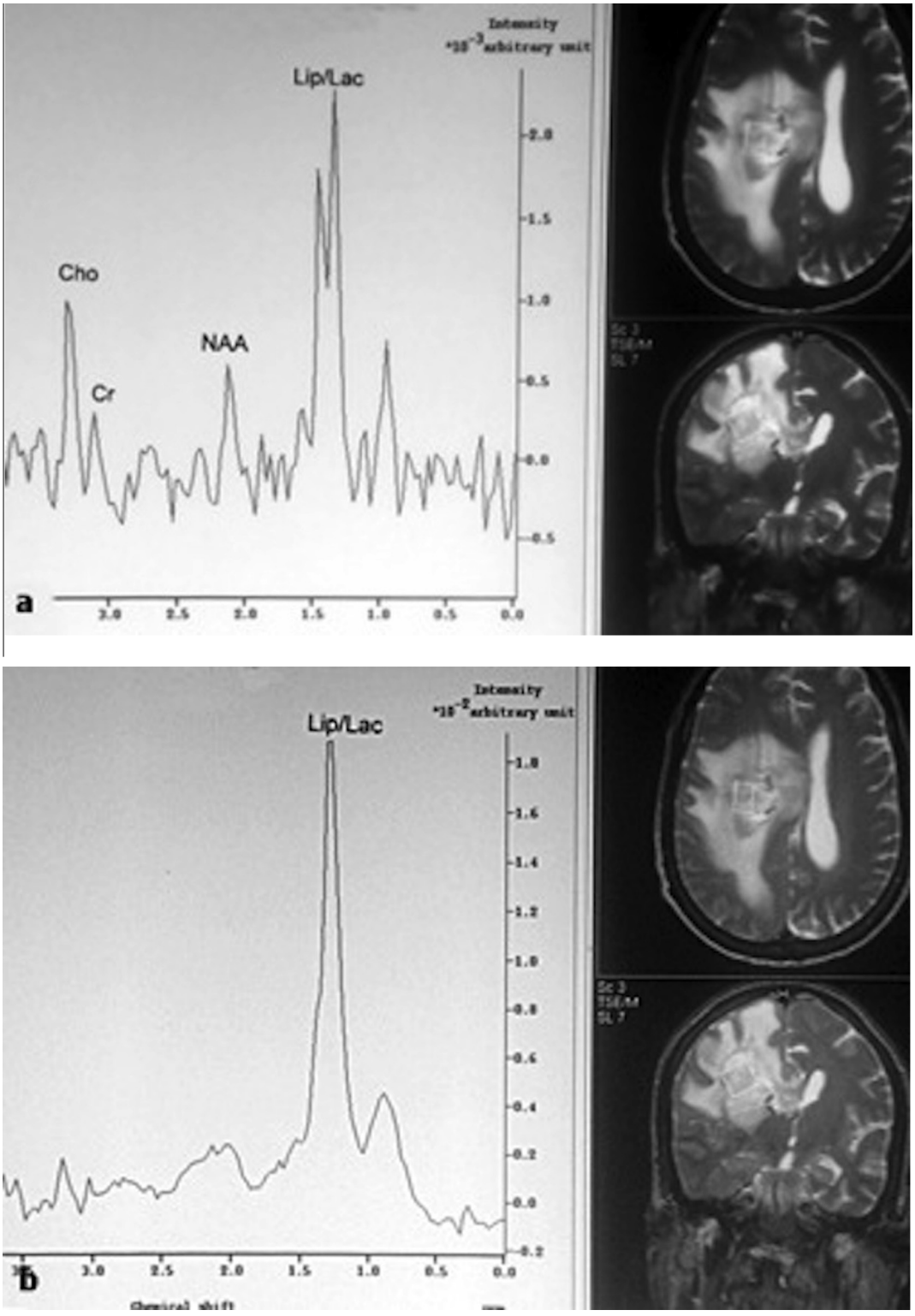

Fig. 1 Twenty-three year old patient with a high grade glioma (Glioblastoma multiformis) involving the right temporo-parietal region that was predominantly cystic. A single voxel ($1 \times 1 \times 1$ cm) was placed on a solid component. (a) MRS obtained at long TE (288) showing mildly elevated Cho, decreased NAA, with estimated Cho/NAA:170, Cho/Cr:17 and NAA/Cr:0.1. (b) MRS obtained at short TE (31) showing no MI, very high levels of Lipid/lactate peak denoting tumor necrosis.

astrocytoma (0.39 ± 0.15) and GBM (0.025 ± 0.06) (Figs. 1–3) (Table 1).

Of the 22 patients with verified gliomas, 21 were correctly classified, with one false-positive case who was misdiagnosed

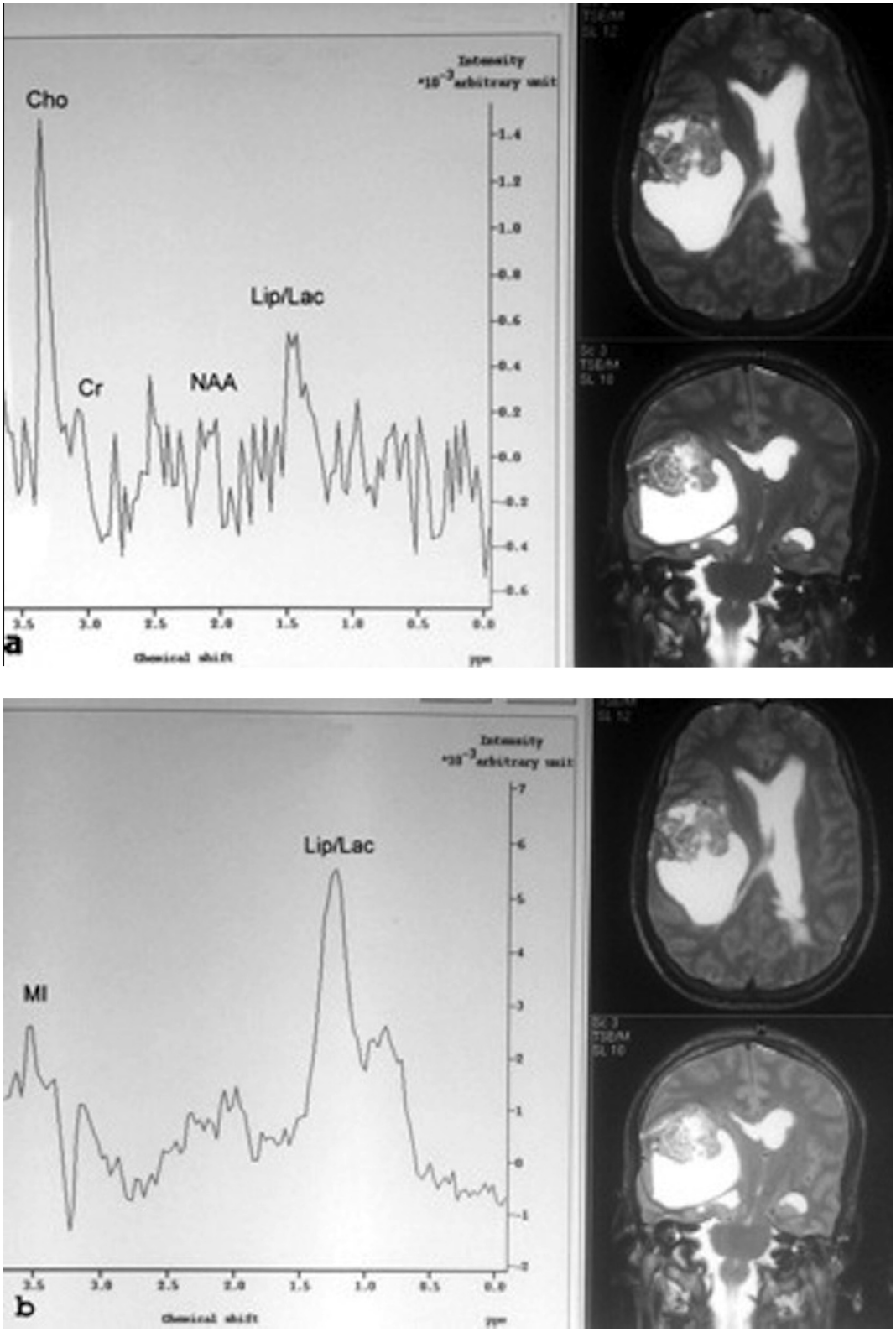

Fig. 2 Sixty-three year old patient with a right temporo-parietal intermediate grade glioma (Astrocytoma grade II) with extensive perilesional edema. A single voxel (1 × 1 × 1 cm) was placed on the solid portion. (a) MRS obtained at long TE (288) showing elevated Cho, depressed NAA, with estimated Cho/NAA:1.8, Cho/Cr:5.5 and NAA/Cr:2.9. (b). MRS obtained at short TE (31) showing moderately elevated MI, the MI/Cr:0.39. The lipid/lactate peak is elevated.

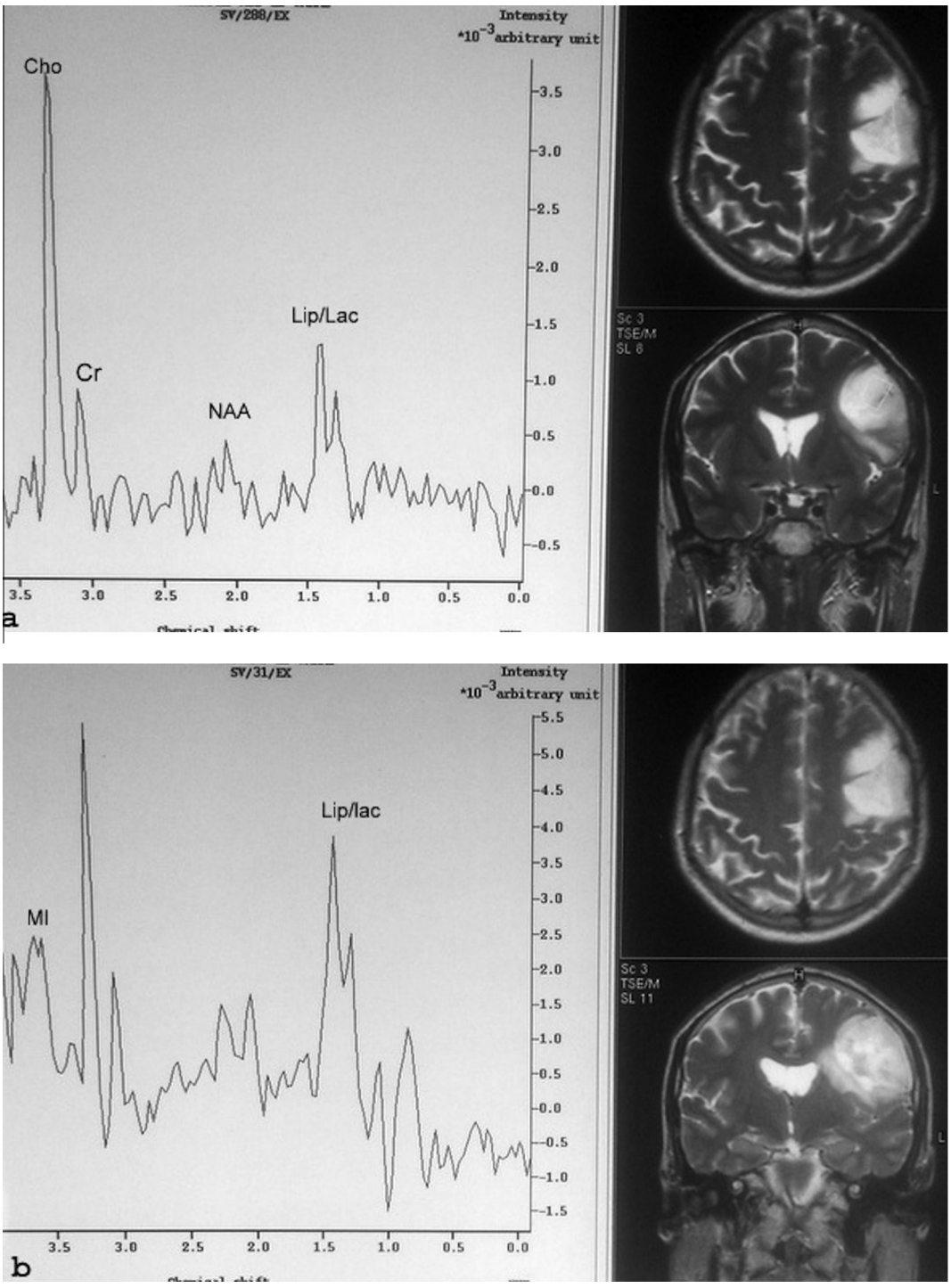

Fig. 3 Fifty-three year old patient with a left temporo-parietal para-sylvian low grade glioma (Astrocytoma grade II) with minimal surrounding edema. A single voxel ($1 \times 1 \times 1$ cm) was placed within the lesion. (a) MRS obtained at long TE (288) showing elevated Cho, depressed NAA, with estimated Cho/NAA:20, Cho/Cr:7.8 and NAA/Cr:0.38. (b). MRS obtained at short TE (31) showing a high level of MI, with estimated MI/Cr:0.97, together with raised Lipid/lactate peaks.

Table 1 Results of MI/Cr ratios derived from magnetic resonance spectroscopy (MRS) with low-grade, intermediate-grade and High-grade gliomas.

	Low grade astrocytoma	Anaplastic astrocytoma	GBM
MI/Cr	2 ± 1.5	0.39 ± 0.15	0.025 ± 0.06
Cho/NAA	9.8 ± 7.8	10.9 ± 8.3	33.34 ± 66

as high grade glioma using MI/Cr ratio and the biopsy revealed grade II glioma.

The diagnostic accuracy, sensitivity and specificity of MI/Cr ratio for the grading of glioma was 95.4%, 100%, 92.8%, respectively.

5. Discussion

Non-invasive grading of gliomas is still considered a challenge despite its important role in the prognosis and management of patients with brain neoplasms (10).

Preoperative grading of gliomas based on conventional MR imaging is often unreliable (11). The radiologic grading of gliomas by conventional MR imaging has a sensitivity ranging from 55% to 83% (5,6). Low and high grade gliomas may be differentiated on conventional MR imaging by characteristic differences in the degree of contrast enhancement and the extent of mass effect and cyst formation, which are more pronounced in higher lesion grades (12). However many high-grade tumors do not show contrast enhancement in the post-contrast images, which may yield a false-negative diagnosis (13,14). This outcome has led to the investigation of advanced MR imaging for grading (11).

The clinical utility of proton MRS in glioma grading is still being investigated. At this point, it is important to understand that MRS is very sensitive to abnormal metabolic changes, but the specificity is relatively low (15). The sensitivity, specificity, and accuracy of MRS in differentiating between high and low grade neoplasms are 100%, 86%, and 96%, respectively (16).

The results of glioma grading by using MRS vary widely. These wide variations may be attributed to different methods and metabolites overlapping between different tumor grades (17).

Previous studies have shown the potential of MRS to differentiate low grade from high grade gliomas (6). They used Cho/Cr, Cho/NAA ratios in the determination of the glioma grade. They had observed higher Cho/Cr and Cho/NAA in high grade compared to low grade tumors, though threshold values of metabolite ratios for grading of gliomas are not well established.

In this series we did not rely on Cho/Cr or Cho/NAA ratio for the grading of glioma, in general we found a high level of Cho in high grade tumors, However high levels for Cho with high Cho/Cr and high Cho/NAA ratios had been observed in some low grade gliomas. This was in concordance with the previous report by law et al. (6) who reported high Cho level in low grade glioma. On the other hand Hall et al. 2001 reported low Cho level ratios in some GBM (18). This may be due to extensive necrosis, which increases the false-positive rates and false-negative rates in predicting low and high grade gliomas, respectively (19).

In this study we used Cho/NAA, Cho/Cr ratios to differentiate brain tumors from nonneoplastic disorders. We confirmed the diagnosis of glioma versus cortical dysplasia and encephalitis in four cases based on elevated Cho/NAA, Cho/Cr together with MI/Cr ratio.

Using short echo MRS (TE 30), MI can also be used to differentiate low and high-grade gliomas (20,21). Low-grade gliomas express higher levels of MI compared with high-grade gliomas. This may be due to the lack of activation of phosphatidylinositol metabolism resulting in the accumulation of MI (19).

Only few publications have evaluated the diagnostic potential of MI/Cr ratio in glioma grading. In this study the tumoral grading was done based on the MI/Cr ratio, we used the results of Castillo et al., as base line for grading. They demonstrated a threshold value of 0.82 ± 0.25, 0.33 ± 0.16, and 0.15 ± 0.12 for MI/Cr ratio in predicting low, anaplastic and high grade tumors, respectively (9).

We were able to differentiate between low grade (II) and high grade (III + IV) gliomas using the MI/Cr ratio. The levels of MI/Cr were higher (2 ± 1.5) in patients with low-grade astrocytoma, and lower in patients with anaplastic astrocytoma (0.39 ± 0.11) and GBM (0.025 ± 0.06).

This was an agreement with Majos and his colleague who reported that MI at short TE provided some separation between low grade astrocytoma and anaplastic astrocytoma. In addition it showed a significant difference between tumor groups which are difficult to differentiate (low grade astrocytoma versus GMB-metastases, and anaplastic astrcytoma versus GMB-metastases) (22).

Aydin et al. tried to make another variation by using Cho/MI for the categorization of tumors according to their malignancy rate and differentiation from non neoplastic lesions. They demonstrated that the Cho/MI ratio is a good diagnostic tool in glioma grading, with the highest Cho/MI ratio found in GBM and lowest Cho/MI ratio found in low grade gliomas (23).

However our results disagreed with the previous reports by Kousi and his colleagues who used 3T 1H-MRS in grading cerebral gliomas at short and long TE in 71 patients with untreated glioma (24). MI was observed to be increased for both glioma grades, the MI/Cr ratio was 0.85 ± 0.24 and 0.90 ± 0.35 for low and high grade gliomas, respectively and hence that ratio did not significantly differentiate the two tumor groups.

Kim et al. (25) also used 3T MR-spectroscopy for the grading of glioma in 35 patients. They found that MI/Cr ratio increased with grade of the tumor with the MI/Cr ratio being 0.86 ± 0.19, 1.23 ± 0.37, 1.15 ± 0.52 for grade II, grade III, and grade IV tumors, respectively (25).

In this study the accuracy of MI/Cr for predicting the glioma grade was high. One case was diagnosed as anaplastic glioma based on the MI/Cr ratio however the biopsy revealed grade II glioma, this may be explained that the biopsy was not necessarily taken within the area of the lesion with greatest cellularity, so it may underestimate the tumor grade (26,27).

In our series one case was diagnosed as low grade astrocytoma, however a follow up MRI done after 1 year showed progressive increase in the size of the lesion, with a newly developed large cystic component, and the pathology revealed mixed astrocytoma grades II and III. This may be attributed either to the increase of the tumor grade over this considerable period of time or depends on the voxel site that was not at the same location of the biopsy site.

Previous studies by Castillo et al. and Smith et al. found that oligodendroglioma and mixed oligoastrocytoma have spectroscopic characteristics similar to high-grade astrocytoma, with high levels of choline, but may also have elevated MI (9,28). In our study we have one case of oligodendroglioma, which showed in addition to the elevated Cho level, mildly elevated lipid/lactate peaks, the MI was elevated as well with the MI/Cr ratio being 0.65.

Lipid and lactate elevation correlate with necrosis in high-grade gliomas and have also been shown to be useful in differentiating low and high-grade gliomas (29). In this study high lipid/lactate peak was observed in 6 cases of high grade GBM cases.

The limitations of the study included small sample size which may reduce or bias the power of the results. Also not all low grade glioma underwent biopsy however they followed up after treatment with radiotherapy. Lastly, because only a single-voxel technique was used, the possibility of sampling errors in tumors of heterogeneous appearance cannot be excluded.

6. Conclusion

MRS has proven to be an important complementary tool saving the patient from unnecessary biopsy taking when it is conclusive thus altering the treatment planning. This study had demonstrated that the MI level and the MI/Cr ratio are important in presurgical grading of brain tumors.

Conflict of interest

The authors declare that there is no conflict of interest.

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