Original Article

Multivoxel MR Spectroscopic Imaging – Distinguishing Intracranial Tumours from Non-neoplastic Disease

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Abstract

Introduction: Multi-voxel MR spectroscopic imaging (MRSI) provides chemical metabolite information that can supplement conventional MR imaging in the study of intracranial neoplasia. Our purpose was to use a robust semi-automated spectroscopic analysis to distinguish intracranial tumours from non-neoplastic disease. Materials and Methods: Twenty intracranial tumours and 15 patients with non-neoplastic disease confirmed on histological examination or serial neuroimaging were studied with 2-dimensional MRSI using point-resolved spectroscopic (PRESS) imaging localisation. Using semi-automated post-processing software, spectra were analysed for peak heights of choline (Cho), creatine (Cr), N-acetyl aspartate (NAA), lactate (Lac) and lipid (Lip). Normalised Cho (nCho) ratios, computed by dividing maximum Cho in the lesion by the normal-appearing brain, were compared between intracranial tumours and non-neoplastic disease. Results: Meningiomas displayed homogenously elevated Cho. Malignant tumours, especially large glioblastoma multiforme, displayed inhomogeneity of metabolites within the tumour. All tumours had elevation of nCho >1 (mean 1.91 ± 0.65), and non-neoplastic diseases had tumour nCho <1 (mean 0.91 ± 0.46), which was significantly lower (P <0.05). Two patients with non-neoplastic lesions, one with subacute cerebral infarction and the other with cryptococcoma, had elevated Cho compared to normal tissue (false positive rate 13%). Conclusion: Using semi-automated MRSI method, a simplified normalised Cho algorithm provides a method to distinguish intracranial tumours from non-neoplastic disease.

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Key words: Brain neoplasm, Magnetic resonance imaging, Nuclear magnetic resonance, Spectroscopy

Introduction

The presence of focal intracranial disease may be due to a variety of diseases, including primary neoplasm, metastatic tumour, abscess, subacute infarction and developmental anomalies. It is important to distinguish tumours from non-neoplastic mimics as the appropriate treatment is very different in each pathology. Although magnetic resonance imaging (MRI) is important for the diagnosis of intracranial disease, sometimes the appearances on conventional contrast-enhanced MRI may not be specific. This limits the accuracy and capability of MRI for distinguishing tumour from non-neoplastic conditions and benign from malignant disease. Therefore, a non-invasive imaging method that can improve the diagnostic accuracy would be desirable, especially in ambiguous or atypical cases, to avoid delay in starting treatment and unnecessary biopsy.

Recent developments in MR spectroscopy (MRS) show great promise in providing additional functional and metabolic information in the study of intracranial tumours and can provide biomarkers of neuronal integrity, cell proliferation or degradation, energy metabolism and necrotic transformation of tissues.[1] Various spectroscopic methods, including single-voxel (SV MRS) and multivoxel MR spectroscopic imaging (MRSI), have been used to study tumour biology, grade gliomas and plan treatment.[2-5] The typical MRS appearances of non-neoplastic intracranial

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pathology such as abscess, tuberculosis and cerebral infarction have also been described,[6-10] which seem to be different from the spectroscopic appearance of neoplasms. MRS should therefore have the potential to distinguish neoplasms from non-tumour pathology. Although there have been a few previous reports,[1,11-14] further research and larger clinical trials are needed to address this important clinical issue. Our group has previously used MRSI to assess intracranial pathology.[4,15] In this report, we studied a mixed group of patients with intracranial space-occupying lesions to test the hypothesis that MRSI can distinguish neoplasms from non-tumour pathology.

Materials and Methods

We retrospectively reviewed a database of patients undergoing MRSI compiled from the Neuroradiology Imaging Database in a large tertiary referral hospital for neurological diseases.[16] Non-consecutive patients with contrast-enhancing lesions, suspicious of neoplasm were selected for the study. Pre-treatment neuroimaging studies including MRSI and conventional MRI studies were reviewed. The data were part of a larger MRS study and was approved by the Institutional Review Board.

Two-dimensional (TR 1500 ms, TE 136 or 144 ms, FOV 24 cm, 16 x 16 or 24 x 24 phase encoding matrices, 10 to 15 mm section thickness) MRSI using point-resolved spectroscopy (PRESS) localisation with automated shim and water suppression (PROBE-P, version 8.3, GE Medical Systems, Milwaukee, WI) was acquired. The localised region of interest (known as the PRESS ROI) was placed to include the tumour visible on conventional MR imaging as well as areas of normal-appearing brain parenchyma, avoiding areas of scalp or skull base contamination.[15] Automatic prescan was performed, followed by MRSI scan as recommended by the manufacturer.

Off-line spectral post-processing was carried out using semi-automated software (Probe 2000, Functool, version 2.33, GE Medical Systems, Milwaukee, WI). Spectra were displayed as grids of nominal voxel size 7.5 x 7.5 x 10 mm and overlaid on the conventional MR image used to plan the study. Spectral peak heights of the main metabolites choline [Cho at 3.2 parts per million (ppm) chemical shift], creatine (Cr at 3.0 ppm), N-acetyl aspartate (NAA at 2.0 ppm), lactate (Lac, an inverted doublet at 1.3ppm) and lipid (Lip at 0.9 and/or 1.2 ppm) were identified and measured by one radiologist (CCTL) using the manufacturer's software, and the voxel containing the highest Cho peak within the tumour was selected. The normalised Cho (nCho) ratios were computed by dividing maximum Cho in the lesion by corresponding values in the normal-appearing brain. As far as possible, normal white matter in the contralateral brain, located in the same spectral row on the grid, was used in order to minimise errors of comparison. Student's *t*-test was used to compare nCho values between intracranial tumours and non-neoplastic disease, and the results were considered significant at the 5% level.

Results

Twenty patients with previously untreated intracranial tumours that were confirmed on histological examination after surgical resection or stereotactic biopsy were studied, including 7 meningiomas, 7 glioblastoma multiforme (GBM) and 6 metastatic tumours from lung, colon and breast carcinoma. There were 15 patients with non-neoplastic diseases, including 8 infective, 4 ischaemic, 1 traumatic and 2 developmental abnormalities that were confirmed on serial neuroimaging, cerebrospinal fluid analysis, treatment response, or histological examination after surgery (3 abscesses and 1 cryptococcoma).

In all patients, the focal intracranial lesions (as defined by conventional MRI) showed abnormal metabolic spectra compared to normal appearing brain tissue. Intracranial neoplasms had higher Cho values compared to normal brain tissue (nCho >1) (Fig. 1 and Table 1). Among non-neoplastic diagnoses, nCho values were not elevated (nCho <1) (Fig. 2) in all patients except 2 – 1 patient with subacute cerebral infarction and another with cryptococcoma. These spectra showed the same metabolic pattern as tumours (false positive rate 13% using nCho >1 as criteria for neoplasm).

Grouped data showed a significantly lower nCho value in non-neoplastic diseases (0.91 ± 0.46) compared to intracranial tumours (1.91 ± 0.65) (Fig. 3). Three meningiomas, 3 GBM and 1 metastasis had only Cho with no NAA or Cr peaks. Lipid was present in GBM, metastasis and abscesses, and lactate was seen in abscess, GBM, infarcts and contusion. All focal lesions showed decreased or absent NAA except 1 patient with gray matter heterotopia.

Discussion

In this study, we found that MRSI could be used to distinguish intracranial tumour from non-neoplastic diseases. The diagnosis of intracranial mass lesions can be complicated by ambiguous neuroradiological findings or atypical clinical symptoms. Neoplasms have a range of contrast-enhancing characteristics, ranging from non-enhancing low-grade gliomas to malignant GBM and metastasis. At the same time, non-neoplastic diseases such as cortical dysplasia and contusion may appear as non-enhancing space-occupying lesions and abscesses or acute infarction may enhance and cause mass effect (Fig. 2). In these cases, MR spectroscopy has the potential to non-invasively provide additional metabolic information to improve pre-surgical diagnosis, study disease extent and direct anatomical placement of surgical biopsy.[17] On many clinical MR scanners, MRS can be acquired as an additional

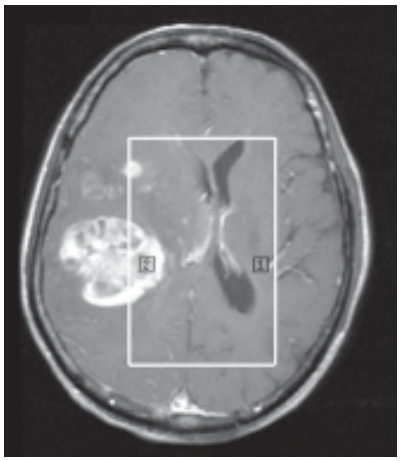

Fig. 1. A

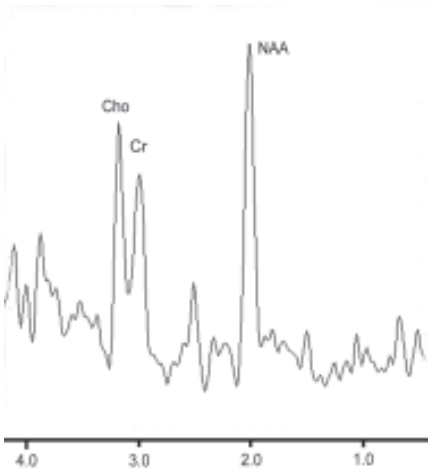

Fig. 1. B

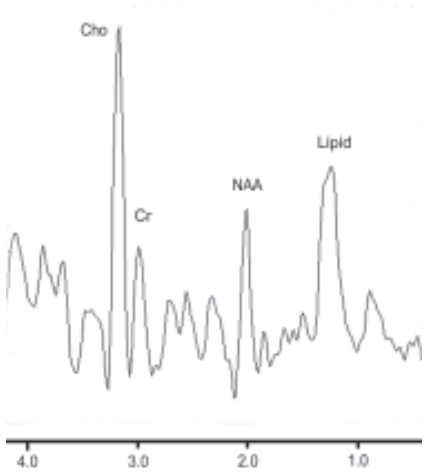

Fig. 1. C

Fig. 1. A 70-year-old man with glioblastoma multiforme. Conventional contrast-enhanced MR image showing irregularly enhancing mass. Spectra showing elevated choline in selected tumour voxels 1B compared to normal 1C.

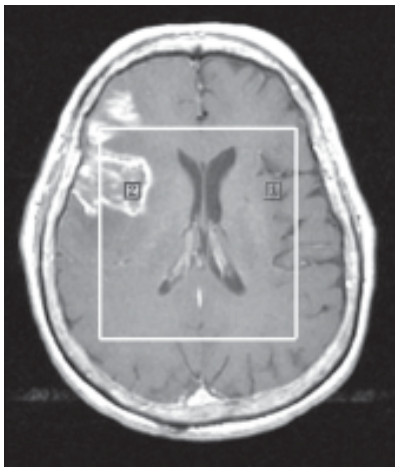

Fig. 2. A

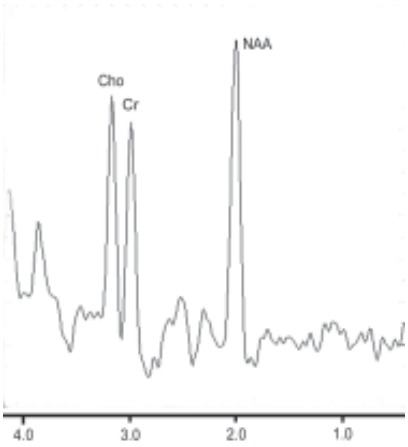

Fig. 2. B

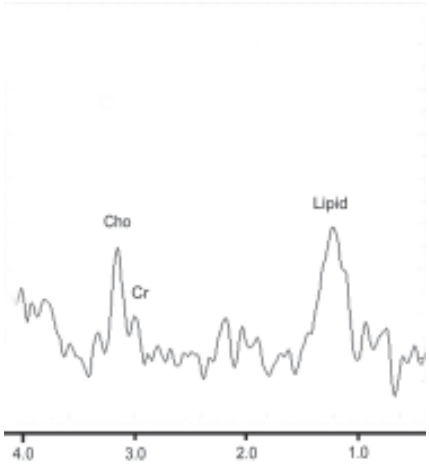

Fig. 2. C

Fig. 2. A 67-year-old woman with subacute approximate 6 days post cerebral infarction. Conventional contrast-enhanced MR image showing irregularly enhancing mass. Spectra showing decreased choline in selected tumour voxels 1B compared to normal 1C.

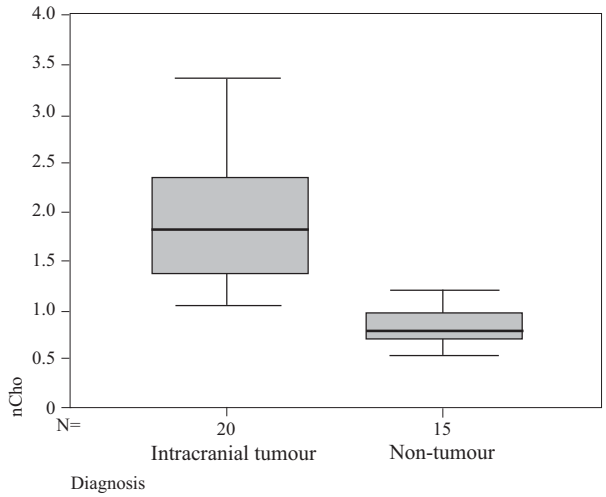

Fig. 3. Boxplot of nCho. Choline peak heights normalised to normal tissue shows significantly different means between intracranial tumours (1.91 ± 65) and non-neoplastic diseases (0.91 ± 46).

pulse sequence, and contribute to a multimodality study of morphological and metabolic information.[15] Although SV MRS is a rapid method for characterising the metabolic information in a 4 to 8 cc region of interest, it is hampered by poor spatial resolution and does not address the problem of tumour heterogeneity.[18] Multivoxel MRSI is technically more demanding but can potentially provide wider anatomical coverage and better spatial resolution to take into account lesion heterogeneity.[15] In our initial experience, we found that MRSI can be successfully applied in the clinical setting if care is taken to avoid regions of high magnetic field inhomogeneity at the base of the skull, and lipid contamination near the scalp.[15]

We found that nCho could be used as an MRSI biomarker of neoplastic disease. By using a normal brain reference standard that was outside the lesion, we were able to adjust

Table 1. Normalised Choline Ratios in Tumour and Non-neoplastic Diseases

Patient/Sex/Age	Diagnosis on MRI	nCho
1/M/70	Meningioma	2.47
2/F/38	Meningioma	1.04
3/M/85	Meningioma	1.84
4/F/53	Meningioma	1.80
5/F/49	Meningioma	1.39
6/M/50	Meningioma	1.47
7/F/52	Meningioma	1.91
8/F/74	Glioblastoma multiforme	2.82
9/M/61	Glioblastoma multiforme	1.23
10/M/69	Glioblastoma multiforme	2.71
11/M/59	Glioblastoma multiforme	2.21
12/F/69	Glioblastoma multiforme	1.48
13/M/70	Glioblastoma multiforme	1.73
14/M/43	Glioblastoma multiforme	1.26
15/M/75	Metastasis	2.23
16/F/77	Metastasis	1.23
17/M/40	Metastasis	1.35
18/M/80	Metastasis	3.36
19/M/57	Metastasis	1.98
20/F/84	Metastasis	2.78
21/M/48	Abscess	0.64
22/M/54	Abscess	0.80
23/M/44	Abscess	0.78
24/F/78	Abscess	0.56
25/M/25	Tuberculous abscess	0.74
26/M/47	Cryptococcoma	2.47
27/M/20	Neurocysticercosis	0.72
28/M/26	Encephalitis	0.97
29/M/73	Infarction day 3	0.97
30/F/67	Infarction day 6	0.63
31/M/62	Subacute infarction unknown duration	1.19
32/F/54	Chronic infarction week 10	0.68
33/F/11	Contusion	0.71
34/F/36	Grey matter heterotopia	0.85
35/F/9	Grey matter heterotopia	1.00

and control for variations in technical factors and group together different patients for analysis.[16] Previous MRS studies have found that Cho resonances originate mainly from intermediates of phospholipid metabolism such as phosphocholine and glycerophosphocholine, both of which play an important role in structure and function of cell membranes.[1,19] Increased Cho may reflect abnormal processes that result in increased cell turnover such as proliferating tumours.[20] Comparison of Cho levels among gliomas have suggested that MRS may be useful in predicting tumour malignancy and grade.[4] Intracranial tumours also showed decreased or absent NAA and creatine. NAA is a marker of functioning neurons and is decreased in a variety of destructive, degenerative and infiltrative processes.[1] Similarly, decreased creatine, which reflects normal energy metabolism, is a non-specific marker of neuronal dysfunction and may be decreased in a variety of diseases. Previous in-vitro MRS studies have shown that the amount of lipids detected by MRS correlates well with the degree of histological tissue necrosis.[21] Brain lactate is produced under conditions of anaerobic glycolysis and indicates a hypoxic condition as well as hypermetabolic glucose consumption.[22,23] Lipids and lactate are physiologically undetected in the normal brain, and their presence in both tumours and non-neoplastic diseases makes them less useful as discriminators between these 2 groups.

Non-neoplastic brain diseases did not show elevated Cho in most of our patients. Abscesses and other infective diseases demonstrate markedly decreased metabolites and strong lipid resonances,[12] and sometimes lactate. Cerebral infarction also shows a reduction in metabolites (including Cho) and often has prominent lactate resonances.[8,9] However, we found a false positive rate of 13% using the criteria of nCho >1 for tumours. Several previous reports have suggested that increased cellular density from white blood cell infiltrates and reactive astrogliosis in subacute non-neoplastic diseases may be responsible for elevated choline in non-neoplastic conditions such as infection, demyelination and organising haematoma.[23,24] Our patient with crptococcoma had elevated Cho probably due to increased inflammatory cellularity. Further studies with larger groups of patients and better statistical analyses are desirable to determine the accuracy of MRSI, study the heterogeneity of malignant tumours and find out whether other imaging biomarkers might be more useful for studying these patients.[25,26]

Besides a small sample size, our study was also limited in the analysis of metabolites. Other authors have used Cho/NAA and Cho/Cr to distinguish a tumour from non-neoplastic disease. Furthermore, other metabolites such as myo-inositol, glycine, taurine, lipid and lactate may also be useful in studying intracranial neoplasm.[4,26,27] Further studies validate nCho as a reference standard; perhaps incorporating other metabolites may be helpful for a better understanding of the role of MRSI in the assessment of intracranial disease.

Conclusion

Using a semi-automated technique in a clinical scanner, MRSI can provide additional information to help distinguish tumour from non-tumour. With the growing application of

MR spectroscopy as a non-invasive tool to evaluate brain disease, both the pitfalls and limitations of the technique must be borne in mind.

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