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CASE REPORT

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Comparison of MR spectroscopy and MR imaging with contrast agent in children with cerebral astrocytomas

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Abstract We studied 33 patients with astrocytomas of different grades (68 examinations) by magnetic resonance imaging (MRI) and proton MR spectroscopy (^{1}H-MRS). We found that in 80% of the spectra, the presence of signals in the area of 0.8–1.5 ppm, assigned to lipids/lactate in ^{1}H-MR spectra, correlated with signal enhancement after Gd-DTPA administration. We suggest that visibility of lipid/lactate signals could be due to blood–brain barrier damage, which is characterized by contrast agent enhancement.

Key words ^{1}H-MR spectroscopy · Human brain · Astrocytoma · Gd-DTPA enhancement · Lipids · Lactate

Introduction

In vivo proton MR spectroscopy (^{1}H-MRS) is becoming an important part of current MR protocols for brain neoplasms. The previously unconvincing results in the area of ^{1}H-MR spectroscopy in human tumors can be ascribed primarily to the fact that the spectra of tumors are fairly confusing owing to the heterogeneity of the tissue being examined. Thus, spectra obtained in this manner are difficult to evaluate. It is generally accepted that the characteristic features of ^{1}H-MR spectra are: a decrease in the total intensity of signals, indicating a decrease in the total concentration of brain metabolites; a decrease in the relative concentration of *N*-acetylaspartate (NAA) and an increasing relative intensity of trimethyl amine signals (Cho) [11] resulting from the breakdown of neurons; a decrease in creatine and/or phosphocreatine concentration (Cr/PCr) and the presence of a lactate signal (Lac) reflecting changes in energy metabolism. Further, there are several signals that represent compounds for which it is difficult to find appropriate metabolic pathways, e.g. lipids (Lip), alanine (Ala).

The main goal of this technique is to help identify the type of neoplasm and the degree of its malignancy. In the future these ambitious expectations may be fulfilled by hardware/software improvements and also by the use of multiparameter statistical methods, such as principal component analysis (PCA) [2, 3, 10, 13]. Probably the most important role for MR spectroscopy in tumor diagnosis at present is following the tumor's response to

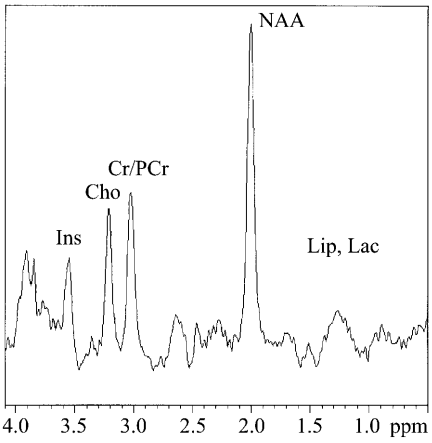

Fig. 1 ^{1}H-MR spectrum (TR/TE/TM=1500/40/20 ms, volume of interest (*VOI*)=27 ml) of a healthy control from the occipital white matter of the brain (*NAA N*-acetylaspartate, *Cr/PCr* creatine/phosphocreatine, *Cho* choline-containing compounds, *Ins* inositols, *Lip* lipids, *Lac* lactate)

treatment or demonstrating evidence of a recurrence of a tumor after surgery.

The purpose of this study is to correlate the results of proton MR spectroscopy and MR imaging (MRI) following the administration of Gd-DTPA, a contrast agent, in children with astrocytomas confirmed by histology.

Patients and methods

Subjects

Overall, 33 young patients between 1 and 15 years old (mean 8.3 years) with astrocytomas of various degrees (grade 1, 7 cases; grade 2, 16 cases; grade 3, 5 cases; grade 4, 3 cases, 2 patients no grade identified) and locations (11 in hemispheres, 12 in cerebellum, and 10 in brain stem) were examined. The protocol was approved by the Grant Ethics Committee.

MR imaging and MR spectroscopy

MR examination was performed using a 1.5-T whole-body imager (Siemens Helicon) equipped with a standard CP head coil. Each examination was performed in three steps:

1. Standard MR imaging using spin-echo sequences (T1-weighted sagittal and coronary images, TR/TE=600/15 ms, slice thickness 3 mm, 4 acquisitions (acq), and T2-weighted transversal images, TR/TE=2500/15/90 ms, slice thickness 5 mm, 1 acq).

2. ^{1}H-MR spectroscopy from the volume of interest (VOI) represented by a cube (8–27 ml) centered in the middle of the tumor; a stimulated-echo sequence (STEAM) was used: TR/TE/TM= 1500/40/20 ms, 256 acq, gradient=2 mT/m for a VOI of 27 ml, 3.5 mT/m for a VOI of 8 ml, 1 or 3 CHESS pulses with pulse width 60 Hz for water signal suppression, spectral width= 2000 Hz.

3. MRI examination using Gd-DTPA (Schering) contrast agent administration (T1-weighted images, see step 1, above).

Evaluation of data

During 68 sessions we obtained 76 ^{1}H-MR spectra prior to application of the contrast agent Gd-DTPA. Spectra were evaluated by standard procedures (eddy current compensation, zero filling of the 1,024 complex time–domain data points to 4,096 data points, Fourier transformation, zero and first-order phase correction and polynomial baseline correction) and printed in standard format in the same scale.

MR spectroscopic results were evaluated by three operators (1 radiologist, 2 spectroscopists). In the MR spectra, three observers monitored areas of lipid and/or lactate signals (0.8–1.5 ppm), and whenever two of them believed a signal was present in the spectrum, the result of the MRS was regarded as positive. If two observers rated the result as nonacceptable, the result was considered a technical error.

A similar approach was used to evaluate MR images. The evaluation of MR images was based on a comparison of T1-weighted MR images from the tumor area before and after contrast administration (Figs. 2a,b and 3a,b). If, after contrast agent administration, two observers rated the signal intensity in the MR image as increased, then the result of the MR image was regarded as positive.

Results

One of the typical ^{1}H-MR spectra (TE=40 ms) of the brain of a healthy volunteer is shown in Fig. 1. These spectra were used for comparison with all the spectra of astrocytomas evaluated in the study (for typical examples, see Figs. 2, 3). We focused our attention on the range of chemical shifts from 0.8 to 1.5 ppm, where characteristic signals of lactate [15], alanine and lipids are observable (Fig. 2). The sequence with TE=135 ms was used for editing of spectra to confirm the presence of lactate. Nevertheless, strong overlay lipid and lactate signals did not allow the quantification of the lactate content.

The spectra were evaluated by using a subjective visual pattern recognition method according to the procedure described in the "Patients and methods" section, and the results were compared with a similar evaluation of T1-weighted MR images. Out of the total of 68 examinations, the results of MR imaging were negative in 29 cases (no enhancement after Gd-DTPA administration) and positive in 39 cases (see Table 1).

The presence or absence of Lip/Lac signals in tumors correlates well with MRI, and the results are summarized in Table 1. Lipid and/or lactate signals were not

Table 1 Summary of the observations in MR imaging and ^{1}H-MR spectroscopy (*MRI positive* finding means contrast enhancement, *MRS positive* finding means visible Lac/Lip)

MRS vs MRI	MRI negative 29 cases	MRI positive 39 cases	Overall agreement of both methods
Agreement	20 (69.0%)	34 (87.2%)	79.4%
Disagreement	6 (20.7%)	1 (2.5%)	10.3%
Technical error	3 (10.3%)	4 (10.3%)	10.3%

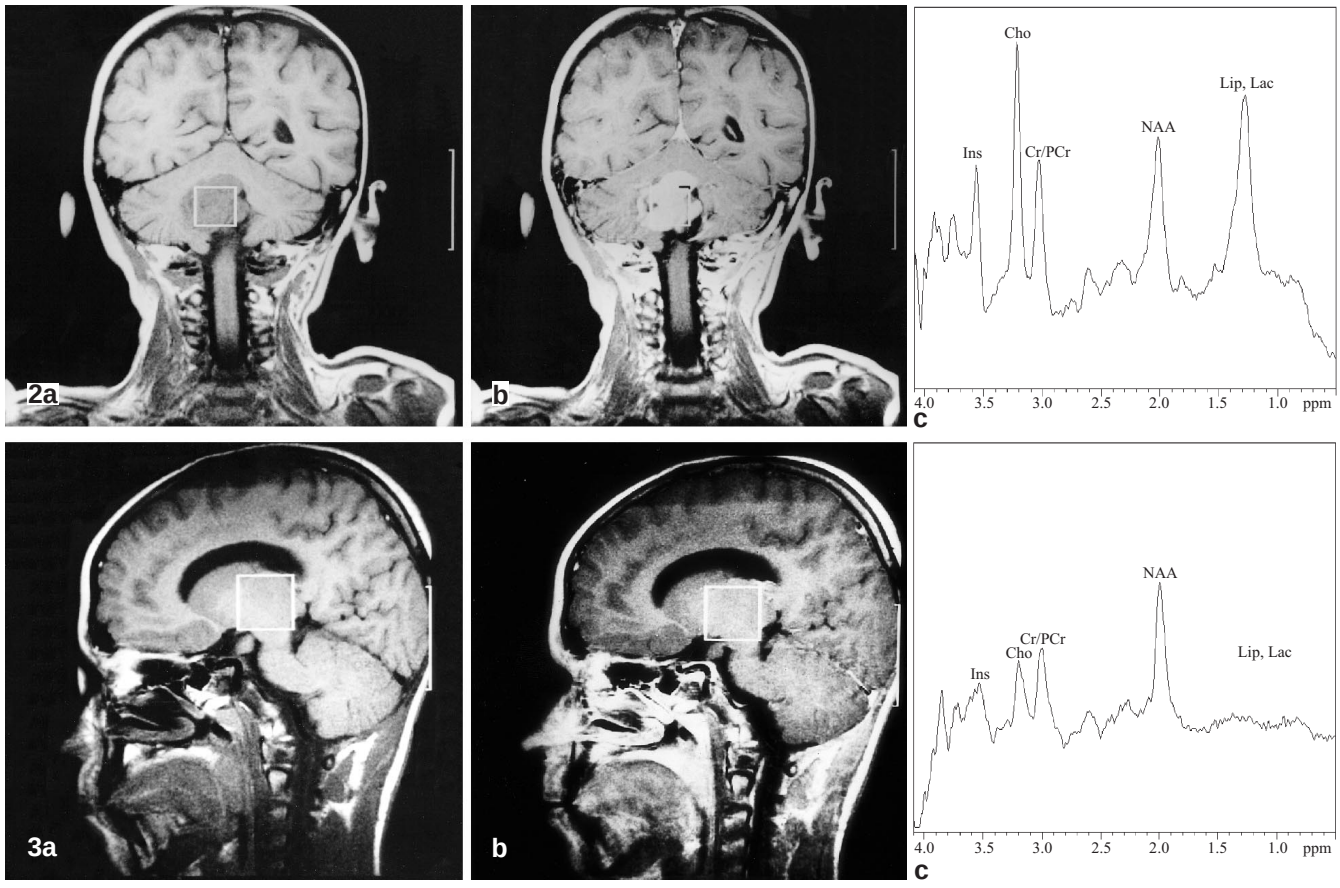

Fig. 2 T1-weighted cross section of the brain of a patient with astrocytoma **a** before and **b** after contrast administration (TR/TE = 600/15 ms). **c** ^{1}H-MR spectrum (TR/TE/TM=1500/40/20 ms, VOI=27 ml) from the defined area in **a** and **b**. The new signals belonging to lipids and/or lactate are visible in the area right of the NAA signal

Fig. 3 T1-weighted cross section of the brain of a patient with astrocytoma **a** before and **b** after contrast administration (TR/TE=600/15 ms). **c** ^{1}H-MR spectrum (TR/TE/TM=1500/40/20 ms, VOI=27 ml) from the defined area in **a** and **b**. In this patient no signals belonging to lipids and/or lactate are visible

found in 69% of negative MR images, that is to say when no increase in the signal intensity was seen. Signals in the MR spectra were seen in 21% of negative cases, while the remaining 3 examinations (10%) were not assessed because of the low technical quality of the spectra.

Similar results were obtained for positive MRI findings of tumors, with agreement between MR images and spectroscopy found in 87% of the cases. Only in 1 case were no signals of Lip/Lac seen; 10% of cases were classified as technical error.

Overall, agreement between the results of MRI and of ^{1}H-MR spectroscopy was found in almost 80% of the 68 examinations. In 10% the results were not consistent, and the correlation was not evaluated in 10% for technical reasons.

Discussion

The presence of a lactate signal in the spectrum was originally regarded as one of the criteria characterizing the degree of malignancy [7]. Recently, many studies have confirmed that the signal is not regularly observed in the spectra of tumors and its presence does not necessarily have to be a marker of a neoplasm. Furthermore, the lactate signal often overlaps with broad signals of lipids, and lactate detection does not necessarily have to be unambiguous even when editing techniques are used [5, 6, 8]. We found signals in this range in 59% of the examinations, which is in reasonable agreement with the results of a multicenter study in which Lac/Lip signals were observed in 41% of astrocytic tumors studied [12].

The contrast enhancement observed in T1-weighted images after the administration of Gd–DTPA is known as a marker of a damaged blood–brain barrier (BBB). It is also known that in some astrocytomas, the enhancement coming from the area of the tumor is not seen after the application of a contrast agent. Similarly, not all the

Table 2 Hypothesis for different findings in ^{1}H-MR spectroscopy and MR imaging (BBB blood–brain barrier)

	A	B	C	D
MRI with Gd-DTPA	Negative	Positive	Negative	Positive
Lipids or lactate in the MR spectrum	Negative	Positive	Positive	Negative
Brain tissue status	Neuronal damage	BBB damage	Necrosis	?
No. of examinations	20	34	6	1

MR spectra of astrocytomas exhibit distinct differences from the spectra of a healthy brain except for a decrease in the total signal intensity. Such examples are shown in Fig. 3b,c.

Mobile lipid signals observable in proton spectra [4] probably arise from a membrane breakdown [16] that is directly or indirectly connected with the presence of macrophages, inflammatory cells, edema, neoplastic cells or damaged membranes of degenerating cells.

The contrast enhancement of Gd-DTPA is detectable in the brain when the BBB does not function properly. Since glial cells comprise an important part of the BBB, their necrosis may explain both the leakage of the contrast agent across the barrier and the lipid signal arising from the necrotic tissue. It is this fact that points to a possible correlation between the Lip/Lac signals seen in the proton spectra and the enhanced contrast of the tumor and that led us to formulate our hypothesis explaining our results. The hypothesis is based on a description of the status of the cells in the tumor and its surroundings (Table 2).

If nerve cells are damaged by a tumor, or if there are tumor cells without necrosis and no damage to the BBB, then no lipid or lactate signals in the spectra or contrast-induced tumor enhancement can be seen (case A). If the BBB does not function properly and the damage to the BBB is caused by the necrosis of cells contributing to the integrity of the BBB, the lipid signal is present in the spectra and the signal intensity of the tumor is enhanced after the administration of the contrast media (case B). If necrosis does not destroy cells contributing to the BBB, Lip/Lac signals can be noted in the tumor area as in the preceding case, but the contrast agent does not cross the BBB and thus no contrast enhancement is noted (case C). In the last case (D), no Lip/Lac signals are observed in the proton spectrum although MRI signal enhancement is seen. We can speculate that in this case the breakdown of the BBB is caused by mechanisms other than necrosis or that the BBB in the tumor area was originally underdeveloped.

This theory is supported by in vitro high resolution MR findings: Kuesel et al. [9] monitored lipids in astrocytoma extracts and found a correlation between the degree of necrosis and the amount of lipids. Our study confirms their observation that the levels of lipids found in our in vivo MR spectra could be related to the degree of necrosis. In 6 cases we did not observe MRI enhancement after contrast agent administration, while the spectra showed Lip/Lac signals [14].

There are several questions that have to be answered. We are unable to say what type of lipids we observe, and the mechanism of their synthesis is still unclear [9]. In the normal brain the concentration of phospholipids is about 50 mM. The signal of these compounds is broad due to their low mobility and short relaxation times, and there are no characteristic signals that can be assigned in proton spectra. On the other hand, under abnormal conditions, CH_2 and CH_3 signals of fatty acid chains are observable. This is the case in peroxisomal disorders [1] and tumors.

The results emerging from our study suggest that if a signal in the area of Lip/Lac (0.8–1.5 ppm) is present in the proton spectrum, we can expect an enhanced signal intensity in the MR image after contrast agent administration. The presence of these changes may reflect damage to the BBB and co-existing necrosis, which may be pathophysiologically connected.

Conclusions

1. We found a nearly 80% correlation between signal visibility in the area of lipids and/or lactate in ^{1}H-MR spectra and contrast enhancement in MR images after Gd-DTPA administration in patients with astrocytomas. We conclude that MR spectroscopy could be another possible method for describing the state of cells in a tumor area.

2. This correlation could also be characteristic of other types of brain tumors.

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