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## **Metabolic Findings on 3T $^1\text{H}$ -MR Spectroscopy in Peritumoral Brain Edema**

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# Metabolic Findings on 3T <sup>1</sup>H-MR Spectroscopy in Peritumoral Brain Edema

**BACKGROUND AND PURPOSE:** Little is known about the metabolic properties of brain edema associated with tumors. This work was conducted on the basis of the assumption that, in the presence of intra-axial and extra-axial brain tumors, the white matter involved by the edema is a site of metabolic change that involves the structure of the myelin sheath.

**MATERIALS AND METHODS:** Thirteen patients comprised our cohort affected by intra-axial and extra-axial cerebral tumors with a peritumoral T2-weighted MR signal hyperintensity as a result of edema, where MR spectroscopy showed no increase in choline-containing compounds. Measurements on proton MR spectroscopy (<sup>1</sup>H-MR spectroscopy) were performed with a 3T whole-body scanner with use of a point-resolved spectroscopy sequence for localization (TR, 2000 ms; TE, 35 ms), and the metabolites were quantified with the SAGE method. Peak intensities of the main metabolites were expressed as ratios of one another and were compared with values obtained in the white matter of the left frontal region in a control group of 16 healthy volunteers.

**RESULTS:** Choline-to-creatine (Cho/Cr) and myo-inositol-to-creatine (mIns/Cr) signal intensity ratios were normal in all patients. *N*-acetylaspartate-to-creatine (NAA/Cr) and *N*-acetylaspartate-to-choline (NAA/Cho) ratios decreased in 4 patients. Glutamate plus glutamine-to-creatine (Glx/Cr) was increased in 10 patients. A resonance peak at 3.44 ppm, strongly suggesting the presence of glucose, was detected in all but 1 patient. Lactate was detected in 12 patients and lipids in 5. Moreover, the resonances that pertained to the aliphatic amino acids valine, leucine, and isoleucine were present in 12 patients.

**CONCLUSIONS:** Our findings on MR spectroscopy confirmed the hypothesis that in the edema surrounding brain tumors, an energy-linked metabolic alteration was associated with injury to the myelin sheath.

**B**rain tumors are very often associated with perilesional edema. The pathophysiologic mechanisms at the base of its formation<sup>1,2</sup> are related to ischemia caused by compression of the tumor,<sup>3</sup> stasis followed by venous congestion,<sup>4</sup> and excretory-secretory phenomena.<sup>5-8</sup> Although the pathogenesis of the edema differs according to whether the tumor is intra-axial or extra-axial, ultrastructural studies have shown that, in both cases, the edema is vasogenic.<sup>9</sup> The advent of functional MR techniques such as diffusion and perfusion imaging and spectroscopy has opened the door to in vivo dynamic and metabolic assessments.<sup>10-13</sup> MR spectroscopy studies have investigated brain edema in experimental models<sup>14,15</sup> and in the clinical setting with the use of 1.5T systems.<sup>16-22</sup> MR spectroscopy has been boosted further by the clinical application of high-field-strength devices by offering the advantages of better signal-to-noise ratio and increased spectral resolution, thereby disclosing more metabolites and extending the range of metabolic information.<sup>23</sup>

The aim of our study was to investigate by 3T <sup>1</sup>H-MR spectroscopy the metabolic properties of the brain tissue involved by the edema associated with intra-axial and extra-axial tumors and characterized by signal hyperintensity in MR T2-weighted sequences, to look for a specific metabolic pattern in the edema. Indeed, our hypothesis is that the structure of the

white matter involved by metabolic alteration, more or less reversible, is precisely the myelin. This study was conducted on the basis of the reasonable assumption that the areas of the brain we examined were not affected by proliferation of neoplastic cells, because no increase in choline (Cho)-containing compounds was detected.

## Patients and Methods

### Subjects

Thirteen patients (8 men and 5 women) comprised our cohort. They were between 35 and 67 years old (mean age, 53 ± 8 years) with intra-axial or extra-axial supratentorial tumors, all with perilesional edema in which no increase in Cho relative content was detected by MR spectroscopy. We obtained written informed consent from all patients before we began the examination, and our local institutional review board approved the study.

Eleven patients underwent surgery with the following histologic diagnoses: 7 glioblastomas, 1 metastasis, and 3 meningiomas. Two patients, not surgically treated, were affected by metastases because of the presence of a primary distant tumor with multiple brain lesions. According to Chernov et al,<sup>12</sup> the extension of perilesional edema evaluated by T2-weighted MR images was graded as mild in 2 patients, moderate in 6, and severe in 5. All patients received dexamethasone as the only anti-edema drug.

### MR Protocol

We performed all MR imaging and localized single-voxel <sup>1</sup>H-MR spectroscopy measurements with a 3T whole-body scanner (GE Medical Systems, Milwaukee, Wis). Our standard routine clinical protocol involved use of the standard 8-channel phased array head coil, which

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allowed the best signal-to-noise ratio for MR imaging and MR spectroscopy.

MR imaging was performed with T2-weighted fast spin-echo (FSE) sequences (TR, 4200 ms; TE, 93 ms; NEX, 2; 24-cm field of view; 512 × 512 matrix; 4-mm sections), fluid-attenuated inversion recovery (FLAIR) sequences (TR, 9002 ms; TE, 91 ms; NEX, 2; 24-cm field of view; 320 × 320 matrix; 4-mm sections) in the axial plane, and T1-weighted spin-echo (SE) sequences (TR, 560 ms; TE, 18 ms; NEX, 2; 24-cm field of view; 384 × 224 matrix; 4-mm sections) in the sagittal and coronal planes before administration of a contrast agent and coronal and axial planes after administration of a contrast agent.

<sup>1</sup>H-MR spectra were acquired before administration of the contrast agent with a point-resolved spectroscopy sequence (PRESS) for localization, with TR 2000 ms and TE 35 ms, 128 acquisitions, and a 3-pulse chemical shift selection suppression (CHESS) sequence to provide water suppression.

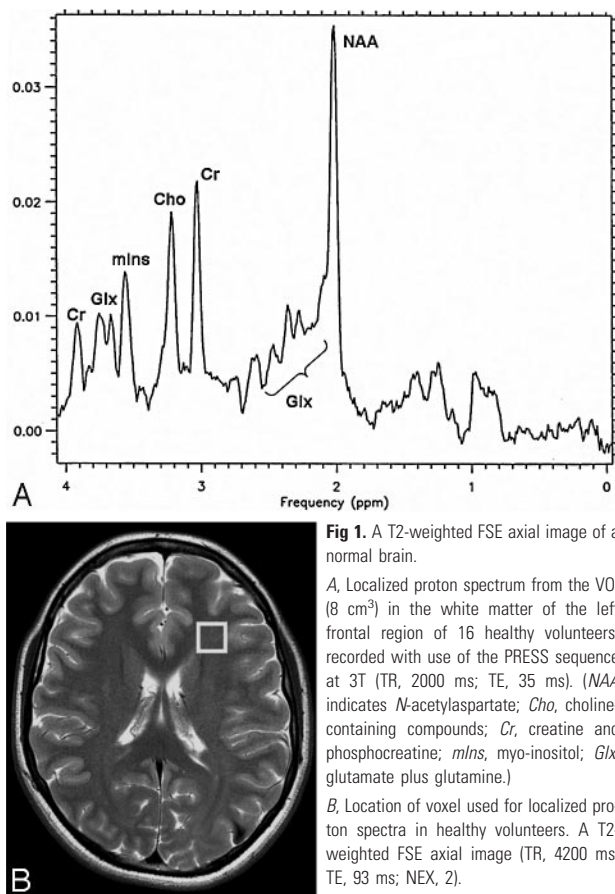
For each spectrum, we collected 16 additional acquisitions with unsuppressed water for phase correction of the metabolite spectra. We used automated optimization of gradient shimming, transmitter pulse power, and water suppression. In all cases, the quality of the shimming obtained in the voxel was controlled by the spectral line width (full width of half maximum in Hz) of the unsuppressed water, obtained by the automated optimization sequence before scanning.

The value of the peak intensities of the main metabolites, *N*-acetyl-aspartate (NAA, 2.02 ppm), choline-containing compounds (Cho, 3.22 ppm), creatine and phosphocreatine (Cr, 3.03 ppm), myo-inositol (mIns, 3.56 and 4.06 ppm), and glutamate plus glutamine (Glx, 2.1–2.5 ppm) were expressed as ratios of one another, in the form of NAA/Cr, NAA/Cho, Cho/Cr, mIns/Cr, and Glx/Cr. We compared these ratios with the values obtained in the white matter of the left frontal region of 16 healthy volunteers between 25 and 67 years old (mean age, 40.7 ± 9 years): (NAA/Cr, 1.8 ± 0.3; NAA/Cho, 2 ± 0.4; Cho/Cr, 0.9 ± 0.2; mIns/Cr, 0.6 ± 0.2; and Glx/Cr, 1.8 ± 0.2). Figure 1 shows a T2-weighted FSE axial image of a normal brain with the selected volume of interest (VOI) (B), and the corresponding <sup>1</sup>H-MR spectrum (A).

The VOI, which varied in size from 1.2 to 8 cm<sup>3</sup>, was accurately positioned on T2-weighted FSE axial and T1-weighted SE coronal and sagittal planes over the white matter involved by edema. The size of the voxel and location were chosen in an attempt to minimize the contribution of neoplastic and cerebral tissue without alteration in signal intensity.

### Analysis of Spectra

We analyzed all MR spectra with the Spectral Analysis Program (SAGE; GE Medical Systems) with the following steps. After the 8-channel signals were combined, the estimated phase correction of the unsuppressed water signal intensity was used to phase-correct the corresponding metabolite (water suppressed) signal intensity. The water-suppressed signal intensity was subtracted from the unsuppressed one, and the “pure water signal intensity” obtained was scaled and subtracted from the suppressed signal intensity to obtain the final metabolite spectrum. After performing a Gaussian apodization, we applied the Fourier transform to the data and interpolated the data to obtain a resolution of 2055/4096 Hz per point. Chemical shifts were referenced to the signal intensity of Cho at 3.22 ppm, and peak integration of the real part of the spectrum for NAA, Cho, Cr, mIns, and Glx was performed. In particular, the signal intensity amplitude of the Glx complex was estimated in the frequency range of 2.1–2.5 ppm on



**Fig 1.** A T2-weighted FSE axial image of a normal brain.

A, Localized proton spectrum from the VOI (8 cm<sup>3</sup>) in the white matter of the left frontal region of 16 healthy volunteers, recorded with use of the PRESS sequence at 3T (TR, 2000 ms; TE, 35 ms). (NAA indicates *N*-acetyl-aspartate; Cho, choline-containing compounds; Cr, creatine and phosphocreatine; mIns, myo-inositol; Glx, glutamate plus glutamine.)

B, Location of voxel used for localized proton spectra in healthy volunteers. A T2-weighted FSE axial image (TR, 4200 ms; TE, 93 ms; NEX, 2).

the basis of phantom spectra of solution with 25 mmol/L glutamate and glutamine at physiologic pH.

With regard to the other metabolites detected in our spectra and manually selected, we arbitrarily assigned lactate (Lac, 1.33 ppm), glucose (Glc, 3.44, 3.78 ppm), and lipids (Lip, 1.3, 0.9 ppm) to 1 of 3 grades: low (+), medium (++), or high (+++), on the basis of the ratio of the integral of the metabolite peak to the integral of the unsuppressed water peak.<sup>24</sup> Instead, for valine (Val, 1.00 ppm), leucine (Leu, 0.98 ppm), isoleucine (Ile, 1.04 and 0.9 ppm), and alanine (Ala, 1.47 ppm), we only determined the presence or absence of these metabolites.

### Statistical Method

We analyzed the NAA/Cr, NAA/Cho, Cho/Cr, mIns/Cr, and Glx/Cr ratios with the Kruskal-Wallis test and determined the level of significance at a *P* value of < .05.

### Results

Table 1 summarizes the NAA/Cr, NAA/Cho, Cho/Cr, mIns/Cr, and Glx/Cr ratios obtained in the edema of the 13 patients. The signal intensity ratios of Cho/Cr and mIns/Cr were normal in all patients.

The NAA/Cr ratio was decreased in 4 (30.8%) patients: 3 with glioblastomas and 1 with meningioma. The NAA/Cho ratio was decreased in 4 (30.8%) patients: 3 with glioblastomas and 1 with metastasis. The Glx/Cr ratio was increased in 10 (77%) patients: 4 with glioblastomas, all with metastases and meningiomas.

Analysis of the NAA/Cr, NAA/Cho, Cho/Cr, and Glx/Cr ratios with the Kruskal-Wallis test failed to reveal statistically signif-

**Table 1: Ratios of the main metabolites detected in the cerebral edema of 13 patients\***

	NAA/ Cr	NAA/ Cho	Cho/ Cr	mIns/ Cr	Glx/ Cr
Glioblastomas (pt no.)					
1	1.7	1.6	1.1	0.8	1.8
2	0.9†	0.9†	1	0.6	1.6
3	2	2.2	0.9	0.7	2.2†
4	1†	1†	1	0.6	2.1†
5	1.2†	1.4†	0.9	0.7	2.6†
6	1.5	1.7	0.9	0.5	2
7	1.5	1.9	0.8	0.5	2.8†
Metastases (pt no.)					
8	1.8	1.7	1	0.4	2.8†
9	1.9	2.3	0.8	0.4	3†
10	1.6	1.4†	1.1	0.4	2.7†
Meningiomas (pt no.)					
11	1.8	1.9	0.9	0.4	3.2†
12	1.9	1.8	1	0.7	3.7†
13	1.4†	1.8	0.8	0.4	2.5†

**Note:**—NAA indicates *N*-acetylaspartate; Cr, creatine and phosphocreatine; Cho, choline-containing compounds; Glx, glutamate plus glutamine; mIns, myo-inositol.

\* Ratios of the main metabolites are detected by PRESS sequences (TR, 2000 ms; TE, 35 ms) in edema surrounding 7 glioblastomas, 3 metastases, and 3 meningiomas. These values were compared with those obtained in the white matter of the left frontal region with use of the same technique in 16 healthy volunteers between 25 and 67 years old (mean age, 40.7 ± 9 years). The normal values are NAA/Cr 1.8 ± 0.3; NAA/Cho 2 ± 0.4; Cho/Cr 0.9 ± 0.2; mIns/Cr 0.6 ± 0.2 and Glx/Cr 1.8 ± 0.2.

† Altered values.

**Table 2: Detection of metabolites normally not found in the human brain**

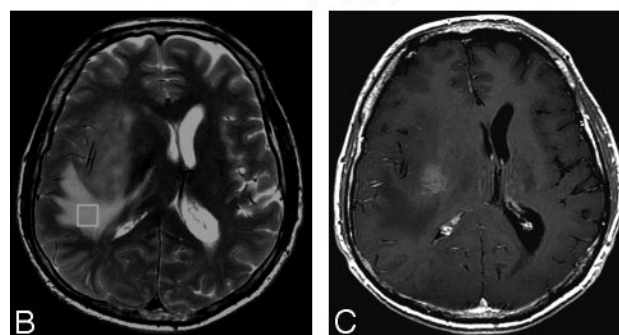
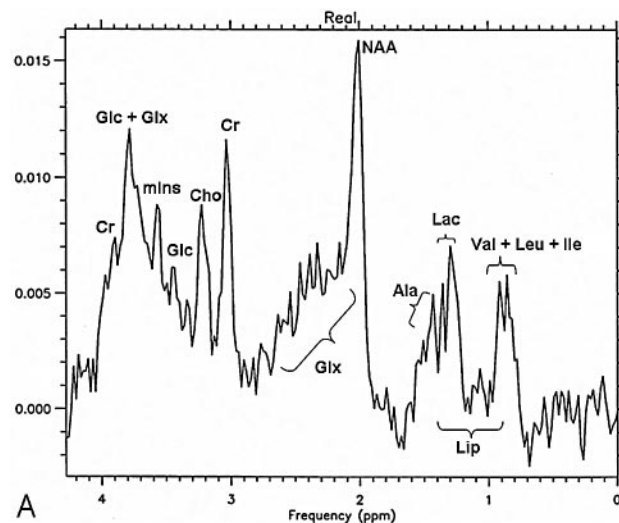
	Glc 3.44 ppm*	Lac*	Lip*	Other Metabolites*
Glioblastomas (pt no.)				
1	++	+		Val, Leu, Ile
2		+	+	Val, Leu, Ile
3	+	++	+	Val, Leu, Ile, Ala
4	+	+		Val, Leu, Ile
5	++	+		
6	+	+	+	Val, Leu, Ile
7	+			Val, Leu, Ile
Metastases (pt no.)				
8	++	+		Val, Leu, Ile
9	+	+		Val, Leu, Ile
10	+	+		Val, Leu, Ile
Meningiomas (pt no.)				
11	+	++	+	Val, Leu, Ile
12	+++	++		Val, Leu, Ile
13	++	+	+	Val, Leu, Ile, Ala

**Note:**—Glc indicates glucose; Lac, lactate; Lip, lipids; Val, valine; Leu, leucine; Ile, isoleucine; and Ala, alanine.

\*Peak resonances of Glc, Lac, and Lip detected and arbitrarily assigned to 1 of 3 grades, low (+), medium (++), or high (+++) on the basis of the ratio of the integral of the metabolite peak to the integral of unsuppressed water peak. For Val, Leu, Ile, and Ala, only their presence is indicated.

icant values associated with the different types of tumors (NAA/Cr,  $P = .28$ ; NAA/Cho,  $P = .33$ ; Cho/Cr,  $P = .94$ ; Glx/Cr,  $P = .05$ ). Instead, there was a significant difference among the 3 groups with regard to the mIns/Cr ratio ( $P = .03 < .05$ ). The significant difference according to the usual statistical tests for multiple comparisons was between the gliomas and metastases.

As shown in Table 2, the resonances of the aliphatic amino acids Val, Leu, and Ile were present in 12 (92.3%) patients: 6 with glioblastomas, all with metastases and meningiomas. Ala was detected in the edema of 2 (15.4%) patients affected by a glioblastoma and a meningioma.



**Fig 2.** A glioblastoma in patient 3.

A, Localized proton spectrum of the edema surrounding the large temporofrontal glioblastoma. The NAA/Cr, NAA/Cho, Cho/Cr, and mIns/Cr ratios are in the normal range. The Glx/Cr ratio is increased to 2.2 (normal value, 1.8 ± 0.2). Glc (3.78 and 3.44 ppm), Lac, Lip, Val, Leu, Ile, and Ala are detected.

B, Axial FSE T2-weighted image (TR, 4200 ms; TE, 93 ms; NEX, 2) with the location of the voxel (6.4 cm³) in the edematous tissue.

C, Axial SE T1-weighted image (TR, 560 ms; TE, 18 ms) after administration of contrast agent. At this level, the upper part of the tumor can be seen.

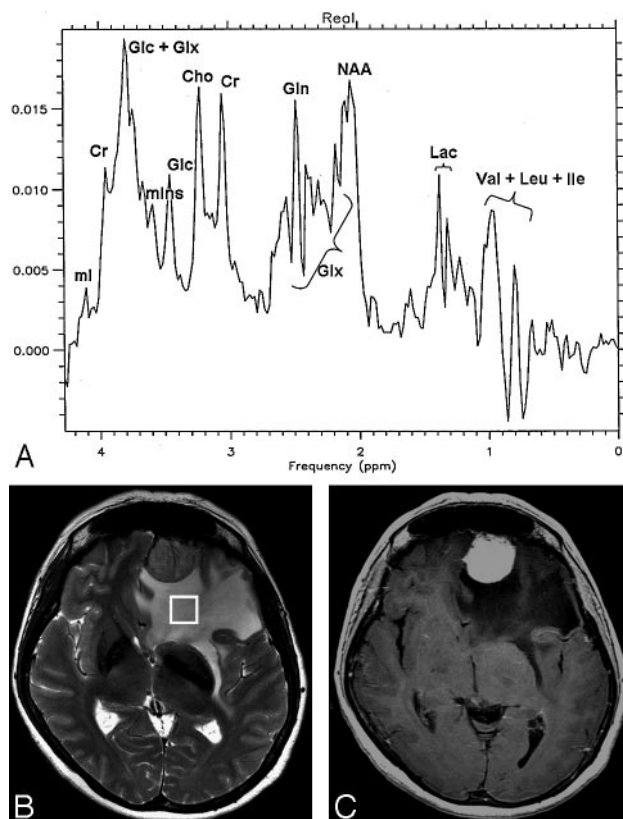
Lac was found in variable amounts in 12 (92.3%) patients: 6 with glioblastomas, all with metastases and meningiomas, and Lip in 5 (35.5%) patients: 3 with glioblastomas and 2 with meningiomas. Figures 2A and 3A show the MR spectra corresponding to the edematous tissue in patient 3, affected by a glioblastoma (Fig 2, B-C), and in patient 12, affected by a meningioma (Fig 3, B-C).

As shown in Fig 3A, in the region of the resonances between 2.1 and 2.5 ppm, relative to the Glx complex, a strong signal intensity centered at 2.44 ppm was present and assigned to glutamine.<sup>25</sup> This resonance was present in noticeable intensity in 6 (46.2%) patients: 1 with glioblastoma, 2 with metastases, and all with meningiomas.

Moreover, an intense broad signal intensity between 3.6 and 3.8 ppm was found in all patients. This resonance usually arises from the  $\alpha$ -hydrogens of amino acids (such as, for example, Glx), from mIns and other metabolites, such as mannitol and Glc. Mannitol, not present in the healthy brain, can be detected if administered as an anti-edema drug, but we can exclude its presence in our spectra because the patients did not receive it.

The presence of Glc was confirmed by the second peak of this metabolite at 3.44 ppm,<sup>26,27</sup> as clearly shown in Figs 2A and 3A.





**Fig 3.** A meningioma in patient 12.

A, Localized proton spectrum of the edema surrounding the meningioma. The NAA/Cho, Cho/Cr, and mIns/Cr ratios are in the normal range. NAA/Cr is decreased to 1.4 (normal value,  $1.8 \pm 0.3$ ), and Glx/Cr is increased to 2.5 (normal value,  $1.8 \pm 0.2$ ). Glc, Lac, Lip, Val, Leu, and Ile are detected.

B, Axial FSE T2-weighted image (TR, 4200 ms; TE, 93 ms; NEX, 2) with the voxel ( $8 \text{ cm}^3$ ) location in the edematous tissue.

C, Axial SE T1-weighted image (TR, 560 ms; TE, 18 ms) after administration of contrast agent with strong enhancement of the tumor.

However, taurine also had a resonance peak at 3.4 ppm. Nevertheless, we excluded the presence of this metabolite because the relative concentration of Cho was normal in all our patients. In fact, the second peak of taurine at 3.2 ppm, if present, would determine the increase in the relative concentration of Cho. As a consequence, Glc was also detected in 12 (92.3%) patients: 6 with glioblastomas, all with metastases and meningiomas.

## Discussion

Edematous brain tissue associated with extra-axial tumors, such as meningiomas or metastatic neoplasms, usually is not involved by tumoral infiltrations. Conversely, in the case of gliomas, the surrounding edematous area is infiltrated by tumoral cells, even beyond the area of enhancement.<sup>28</sup> On this basis, Chiang et al<sup>29</sup> were able to differentiate by MR spectroscopy between high-grade gliomas and solitary metastases on the basis of their different Cho/Cr ratios.

In our cohort, it should be noted that the Cho/Cr signal intensity ratio was normal in the edematous tissue of all the patients and also in the edema associated with glioblastomas. This means that in the analyzed VOIs, no evidence of cell proliferation was found, which allowed us to assert that the patients had only edema.

The most recurrent metabolic findings associated with cerebral peritumoral edema are decreased NAA and the appearance of lactate (Lac).<sup>12,19,20,22</sup> In particular, Chernov et al<sup>12</sup> examined peritumoral brain tissue and found a significant reduction in the NAA/Cr and NAA/Cho ratios and a more frequent presence of Lac compared with the healthy brain. In their study, the NAA level was lowest in cases with a higher content of Lac in the lesion than in the perilesional brain tissue, which suggests that Lac diffuses from tumoral into peritumoral tissue. In the opinion of these authors, the decrease in NAA might have corresponded to the neuronal alteration responsible for associated epilepsy.

Also in our study, nearly all the patients (92.3%) had Lac in the edema, whereas the decrease in the relative concentration of NAA occurred only in 30.8% of the patients. Although we cannot exclude that the reduction in the relative concentration of NAA correlates with the presence of Lac, we have to take into account also that the administration of dexamethasone may be responsible for the metabolic alteration itself.<sup>30</sup>

In our cases, MR spectroscopy of the areas of the tumor (data not shown) revealed that Lac was present in 5 neoplasms (all meningiomas and 2 glioblastomas). In the spectra of the other tumors, lactate was not assessable because of the presence of intense resonances of mobile lipids related to extensive tumoral necrosis. However, its presence could not be excluded. Therefore, we cannot rule out that Lac in edema is the result of diffusion from the tumor, according to Chernov.<sup>12</sup>

To our knowledge, there are no published studies of MR spectroscopy reporting the presence of Glc in brain edema. Although this metabolite has been detected on <sup>1</sup>H-MR spectroscopy in patients with diabetes,<sup>31,32</sup> none of the patients in our cohort had diabetes mellitus. Therefore, Glc seems to be a feature of edema.

Both Glc and Lac are claimed to be integral and important entities of metabolism of cerebral energy.<sup>33</sup> Lac plays an important role in the metabolism of cerebral oxidative energy, as does Glc.<sup>33,34</sup> Lac is oxidized by neuronal mitochondria, and its presence inhibits the consumption of Glc, which therefore accumulates in the tissue.<sup>33</sup> This theory would account for the concomitant presence of Lac and Glc in 11 (84.6%) of our patients.

A very important metabolic change, because it was found in nearly all our patients, was the increase in the Glx complex. This alteration is correlated with neuronal loss and demyelination.<sup>35</sup> Danielsen and Ross<sup>36</sup> claimed that if glutamate exceeds the appropriate concentration as a neurotransmitter, its surplus leads to a toxic effect. It follows that the glutamine-synthetase enzyme would increase to protect the astrocytes by removing the excess glutamate, and this would account for the increase in glutamine that we have seen in our spectra.

In addition, the resonances assigned to mobile lipids were found in 5 (38.5%) of our patients. The presence of lipids in <sup>1</sup>H-MR spectra is correlated with changes in the cell membrane with a mobilization of membrane phospholipids.<sup>37</sup> Danielsen and Ross<sup>36</sup> reported that lipids are also associated with myelin, and their mobilization could be related to a structural myelin impairment.

Our study also detected peaks relative to the amino acids Val, Leu, and Ile in 92.3% of patients. A <sup>1</sup>H-MR spectroscopy on people with multiple sclerosis (MS) reported that these substances also correlated with demyelination in MS

plaques.<sup>35</sup> Other MS studies have reported an increased Cho/Cr ratio in plaque during acute disease,<sup>38</sup> and this alteration was related to severe inflammation without demyelination.<sup>39</sup> The fact that the Cho/Cr ratio was normal in all of our patients does not rule out the possibility that the metabolic changes that we documented were associated with tissue damage without inflammation.

If Lac is an energy source for neuronal mitochondria, according to Schurr's theory,<sup>33</sup> the accumulation of Glc and Glx could have a toxic effect with structural myelin impairment, as testified by the presence of amino acids and lipids. This global metabolic alteration can be reversible after resection of a tumor, whereas an irreversible change in the structure of the myelin sheath could explain the persistent MR T2-weighted signal hyperintensity that failed to return to normal after tumor resection.<sup>40</sup> In fact, demyelination can occur secondary to a local mass effect, as reported by Heinz<sup>41</sup> in the case of a patient with a calcified meningioma. This meningioma showed a large hypoattenuated area around the tumor on CT, and results of a biopsy showed demyelination. When signal hyperintensity on MR T2-weighted images persists after tumor resection, irreversible and more severe structural myelin impairment can be hypothesized.

## Conclusions

This study supported the hypothesis that brain tissue involved by edema has intrinsic metabolic properties. 3T <sup>1</sup>H-MR spectroscopy revealed substances such as Glc and amino acids not previously revealed by a lower magnetic field. Our findings suggest that the edema spectra are indicative of energy-linked metabolic damage associated with structural injury, which may or may not be reversible. As the literature correlates these changes to myelin injury, we suggest that myelin is the most involved structural component.

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