In Vivo Proton Magnetic Resonance Spectroscopy for Metabolic Changes of Human Brain Edema

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Abstract

The metabolism of the brain was investigated in eight patients with peritumoral edema, six patients with ischemic stroke, and 28 normal controls using proton magnetic resonance (MR) spectroscopy. The MR studies were performed using a 1.5-T whole-body imaging and spectroscopy system with a 1500-msec repetition time (TR) and a 270-msec echo time (TE). The peak areas for *N*-acetyl-aspartate (NAA), choline-containing compounds (Cho), creatine and phosphocreatine (Cr), and lactate (Lac) were measured, and the NAA/Cr, Cho/Cr, and Lac/Cr ratios were calculated. To quantify and compare the serial spectra, relaxation effects were investigated by acquisitions at two different points (TRs or TEs) and by monoexponential fitting. The normal NAA/Cr and Cho/Cr ratios were 2.76 and 1.09, respectively. Lac could not be identified in normal brains. In ischemic stroke and peritumoral edema, significantly increased Lac/Cr and decreased NAA/Cr ratios were observed. Resolution of peritumoral edema was associated with normalized NAA/Cr ratio and disappearance of Lac. The T_1 relaxation times of the metabolites were similar in normal brain and peritumoral edema, but the T_2 values were significantly shortened. Serial measurements of T_2 values in two patients with peritumoral edema showed gradual normalization corresponding to improvement of the edema. To absolutely quantify metabolite concentrations in edema, changes in relaxation times should be considered.

Key words: brain edema, lactate, *N*-acetyl-aspartate, proton magnetic resonance spectroscopy

Introduction

Brain edema is defined as an abnormal accumulation of fluid within the brain parenchyma and can be classified into two different types depending on pathophysiological mechanism.⁹⁾ The "cytotoxic" type is due to a severe disturbance of cell metabolism associated with anoxia and ischemia. Intracellular concentrations of molecules and sodium are increased, resulting in increased cellular volume and narrowing of the extracellular space. The "vasogenic" type is associated with brain tumors and brain injury resulting from a breakdown of the blood-brain barrier to macromolecules without brain tissue breakdown. Fluid leaks out of brain vessels and accumulates in the extracellular space. Edema is most frequently associated with tumors and ischemic stroke lesions. Peritumoral edema is mainly

vasogenic edema, while almost all stroke lesions cause a combination of vasogenic and cytotoxic edema and result in brain tissue breakdown.²⁾

Proton magnetic resonance (^1H -MR) spectroscopy allows investigation of specific metabolites within tissue *in vivo*, and has yielded important information about the pathophysiological manifestations of some brain diseases.^{1,4,5,11,16)} ^1H -MR spectroscopy of ischemic stroke shows characteristic prolonged increase of lactate (Lac) levels and loss of *N*-acetyl-aspartate (NAA), indicating "neuronal loss."^{1,5,8)} However, the metabolism of peritumoral vasogenic edema has not been evaluated. As differentiation between certain types of brain edema by computed tomography and MR imaging remains difficult, we hope to obtain additional information from ^1H -MR spectroscopy.

We report our ^1H -MR spectroscopy study of metabolic changes in brain edema, particularly peritumoral edema, and discuss the pathophysiological mechanisms causing the spectral changes

corresponding to resolution of the edema.

Materials and Methods

Fourteen patients with brain edema, six with ischemic stroke and eight with peritumoral edema, and 28 normal controls (ranging from 22 to 68 years old) were examined. All ischemic stroke patients had clear, reliable histories with unequivocal clinical data typical of ischemic stroke, and neuroimaging evidence of acute lesions (Table 1). Serial MR imaging and MR angiography showed the main vessels were occluded in all the cases. All tumor patients had undergone tumor removal. Tissue specimen examination revealed meningioma in four cases, glioblastoma in two, metastatic brain tumor in one, and malignant lymphoma in one (Table 2). The peritumoral lesions demonstrated typical histological evidence of brain edema without tumor invasion.

MR imaging and spectroscopy used a 1.5-T Magnetom SP (Siemens, Erlangen, Germany), a whole-body scanner that combines imaging and spectroscopy systems. Multislice images in transverse (repetition time [TR] 2200 msec, echo time [TE] 80

msec, 5-mm slice thickness) and coronal planes (TR 600 msec, TE 15 msec, 5-mm slice thickness) were then obtained to locate the volume of interest (VOI) for spectroscopy. Water-suppressed, localized ¹H spectra were obtained with a sequence of point-resolved spectroscopy. Control data were obtained from a volume in the left parietal region (3 × 3 × 3 cm). The VOI was selected to contain the bulk of the peritumoral or stroke edema and avoid overlapping the tumor and surrounding bone marrow. Care was taken in serial examinations to select the same volume based on anatomical landmarks in the image, although the size and shape of the edema varied. The magnetic field over the VOI was homogenized by adjusting the linear shims to minimize the water signal width. A water signal width of less than 7 Hz was obtained from all the edematous lesions. The water signal was suppressed with chemical shift-selective pulses optimized for the detection of brain metabolites. The signals (free induction decays) of 100 acquisitions were obtained using standard parameters (TR 1500 msec, TE 270 msec). The data obtained were averaged, zero-filled to 2048 data points, and processed by fast Fourier transformation. The areas of the four main peaks due to NAA, choline-containing compounds (Cho), creatine and phosphocreatine (Cr), and Lac were calculated using a computer algorithm with the lower and upper integration limits set manually. The NAA/Cr, Cho/Cr, and Lac/Cr ratios were calculated. The Cr signal was chosen as an internal reference because the intensity appears to be relatively stable under different metabolic conditions in the brain.^{3,12,15)}

Changes in the metabolite signal ratios depend on changes in concentration and in the relaxation rate of individual metabolites. Therefore, a total of four spectra were obtained using combinations of two TRs (1500 and 3000 msec) and two TEs (135 and 270 msec). The relaxation times for the metabolites were estimated from the data using simple monoexponential fitting.

Data are presented as mean values ± SD. Student's *t*-test was used to assess significance, with *p* < 0.001 considered statistically significant.

Results

I. Normal brain

The peaks corresponding to NAA at 2.03 ppm, Cr at 3.02 ppm, and Cho at 3.20 ppm were readily assigned as described previously,^{3,15)} and were fairly constant in amplitude throughout the selected VOI. Lac could not be detected in normal brains. The NAA/Cr and Cho/Cr ratios were 2.76 ± 0.48 and

Table 1 Clinical data and metabolite ratios in stroke edema patients

Case No.	Age/Sex	Poststroke period (hrs)	Area of infarction	NAA/Cr	Cho/Cr	Lac/Cr
1	78/M	6	lt MCA	2.01	3.00	5.02
2	61/M	12	rt MCA	1.99	2.00	4.50
3	70/F	6	rt ICA	1.30	0.87	3.53
4	85/M	24	rt ICA	1.10	1.18	2.11
5	80/F	12	rt ICA	1.00	0.08	6.40
6	74/F	5	lt ICA	1.48	1.57	5.30

ICA: internal carotid artery, MCA: middle cerebral artery.

Table 2 Clinical data and metabolite ratios in peritumoral edema patients

Case No.	Age/Sex	Histology of tumor	Location of edema	NAA/Cr	Cho/Cr	Lac/Cr
7	59/F	meningioma	rt P	1.70	0.62	0.76
8	62/M	metastasis	rt T	2.88	1.93	1.91
9	42/F	meningioma	rt P	2.38	0.63	0.88
10	61/F	lymphoma	rt T	1.80	1.11	0.60
11	27/F	meningioma	lt P	3.40	0.80	0
12	66/M	glioblastoma	lt F	1.33	1.00	2.00
13	42/M	glioblastoma	lt F	1.91	1.05	0.11
14	60/F	meningioma	rt T	0.60	0.61	0

F: frontal lobe, P: parietal lobe, T: temporal lobe.

Table 3 Comparison of metabolite ratios in edema and normal brain

	NAA/Cr	Lac/Cr	Cho/Cr
Normal brain (n = 28)	2.76 ± 0.48	not detected	1.09 ± 0.13
Peritumoral edema (n = 8)	1.92 ± 0.94*	0.78 ± 0.86* [#]	0.97 ± 0.44
Stroke edema (n = 6)	1.48 ± 0.44*	4.47 ± 1.49*	1.57 ± 0.83

Values are mean ± SD. *Significantly different ($p < 0.001$) from normal brain. [#]Significantly different ($p < 0.001$) from stroke edema.

1.09 ± 0.13, respectively.

II. Stroke edema

The results of ¹H-MR spectroscopy of ischemic stroke edema are given in Table 1. The NAA/Cr ratio was significantly lower, and the Lac/Cr ratio significantly higher compared to normal brain (Table 3). Figure 1 shows an MR image of the VOI and spectra for Case 6. Several months after onset, the spectrum shows only a slight Lac peak, and complete absence of NAA, Cr, and Cho.

III. Peritumoral edema

The results of ¹H-MR spectroscopy of peritumoral edema are given in Table 2. The NAA/Cr ratio was significantly lower, and the Lac/Cr ratio significantly

higher than in normal brain. However, the Lac/Cr ratio was significantly lower than in ischemic stroke edema (Table 3).

Four (Cases 7–10) of the eight tumor patients could be followed up with serial ¹H-MR spectroscopy. The Lac/Cr ratio rapidly decreased and the NAA/Cr ratio slowly increased to within normal limits (Fig. 2). Two patients also demonstrated considerable increases in the Cho/Cr ratio (data not shown). Figure 3 shows typical MR images of the VOI and ¹H-MR spectra before and after tumor removal in Case 10.

Normal T₁ relaxation times for Cho, Cr, and NAA were 1250, 1467, and 1527 msec, respectively, while normal T₂ values were 343, 267, and 357 msec, respectively (Table 4). In peritumoral edema the T₁ values were relatively close to normal values, but the T₂ values, particularly for NAA and Cho, were significantly shorter. Serial postoperative measurements of T₂ values in two patients with peritumoral edema showed gradual normalization of the T₂ values corresponding to resolution of the edema (data not shown).

Discussion

¹H-MR spectroscopy gives a better signal-to-noise ratio and spatial resolution than phosphorus (³¹P)-MR spectroscopy, and is therefore a practical method for clinical use. ¹H-MR spectroscopy can pro-

Fig. 1 Case 6 with acute ischemic stroke. *left*: T₂-weighted transverse MR image, showing the VOI for ¹H-MR spectroscopy in the lesion. *center, right*: ¹H-MR spectra 6 hours after onset showing markedly increased Lac and decreased NAA signals (*center*), and 3 months later showing only the Lac signal (*right*).

Fig. 2 Serial changes in Lac/Cr (*upper*) and NAA/Cr ratios (*lower*) in the edematous lesions of Cases 7 (●), 8 (□), 9 (▲), and 10 (○).

vide quantitative data about Cr, Cho, Lac, and NAA in the human brain.

Creatine kinase, which is mainly present in neurons and muscles, converts creatine to creatine phosphate (PCr) although this process is easily reversed under certain conditions. ³¹P-MR spectroscopy only detects the concentration of PCr which easily changes. The physiological meaning of the Cr (creatine and PCr) peak in ¹H-MR spectroscopy is still unclear, but may be used as an internal reference because the intensity of the Cr peak is relatively stable in various diseases.^{3-5,14}

The Cho signal from the phosphoryl- and glycerophosphoryl-choline is an indicator of membrane synthesis and degeneration.^{4,12} An increased Cho signal may reflect the active membrane metabolism associated with brain tumors⁴ and demyelination in multiple sclerosis.^{11,16} Whether the Cho signal is increased in cerebral infarction remains controversial.^{5,12} In our study, peritumoral and

ischemic stroke edemas were associated with both increased and decreased Cho signals. The Cho signal may not be an indicator for peritumoral or stroke edema.

Lac is the end product of anaerobic metabolism and serves as a marker of glycolysis. Lac concentration is markedly increased in cerebral infarction, many brain tumors, and other diseases.^{4,8,11,14,16} A previous study showed stroke patients had persistent high Lac levels for several months after onset.⁵ Our ¹H-MR spectroscopy study of ischemic stroke edema generally confirms this tendency. Hossman⁷ and Hanstock *et al.*⁶ demonstrated accumulation of Lac in experimental vasogenic edema using biochemical analysis and ¹H-MR spectroscopy, respectively. Our study demonstrated that Lac accumulates in peritumoral edema. Our follow-up results suggest that Lac production stops after tumor removal and Lac is washed out and disappears from the lesions.

NAA, discovered by Tallan in 1956,¹⁷ is found in higher concentrations in gray matter than in white matter, and rapidly disappears when neurotoxin kainic acid is injected into neurons.¹⁰ NAA is considered to be a neuronal marker. Decreases in the NAA/Cr ratio are considered to indicate neuronal loss in cerebral infarction, multiple sclerosis, and brain tumors.^{1,3-5,8,11,12,14,16} Our study showed a decreased NAA/Cr ratio in acute edema, which normalized with resolution after treatment. It is quite difficult to explain what the increased NAA signal means since neuronal regeneration in the brain is not generally accepted. Nuclear MR signals are closely related to relaxation effects and the quantity of metabolites. The relaxation times we obtained in normal volunteers were almost the same as in previous reports.^{3,13} Our study found the T₂ relaxation times of metabolites in peritumoral edema, particularly those of NAA, became shorter without significant changes in the T₁ values. The T₂ values may reflect "slow" overall motions of whole and bound molecules. Frahm *et al.*³ claimed that longer T₂ values of metabolites may reflect high mobility. A clear pathophysiological mechanism for the shortening of the T₂ value is difficult to propose, but the shorter T₂ value may reflect lower mobility of neuronal NAA in edematous brain. The decreased NAA/Cr ratio therefore indicates neuronal loss and lower NAA mobility. In contrast, the increase in the NAA/Cr ratio may only indicate greater mobility of the NAA.

¹H-MR spectroscopy can demonstrate metabolic differences between peritumoral edema and ischemic stroke edema. Edematous lesion around tumors may

Fig. 3 Case 10 with brain edema associated with a malignant lymphoma. *upper*: T_2 -weighted transverse MR images before (*left*) and 2 weeks after surgery (*right*), showing the VOI for ^1H -MR spectroscopy. *lower*: ^1H -MR spectra before surgery showing lower NAA peak and slightly increased Lac peak (*left*), and 2 weeks after surgery showing increased NAA and disappearance of Lac signal (*right*).

Table 4 T_1 and T_2 relaxation times of major metabolites in normal brain and peritumoral edema

	T_1 relaxation time (msec)			T_2 relaxation time (msec)		
	Cho	Cr	NAA	Cho	Cr	NAA
Normal brain	1250 ± 250	1467 ± 300	1527 ± 145	343 ± 25	267 ± 69	357 ± 28
Peritumoral edema	1450 ± 135	1524 ± 515	1477 ± 559	$138 \pm 45^*$	170 ± 60	$210 \pm 52^*$

Values are mean $\pm$ SD. *Significantly different ($p < 0.001$) from normal brain.

have a ^1H -MR spectrum with intermediate metabolite ratios between normal and infarcted brain and may recover completely after successful

treatment. However, absolute quantification of metabolites in edematous lesions requires consideration of changes in relaxation time.

References

- 1) Bruhn H, Frahm J, Gyngell ML, Merboldt KD, Hänicke W, Sauter R: Cerebral metabolism in man after acute stroke: New observations using localized proton NMR spectroscopy. *Magn Reson Med* 9: 126-131, 1989
- 2) Fishman RA: Brain edema. *N Engl J Med* 293: 706-711, 1975
- 3) Frahm J, Bruhn H, Gyngell ML, Merboldt KD, Hänicke W, Sauter R: Localized proton NMR spectroscopy in different regions of the human brain in vivo. Relaxation times and concentrations of cerebral metabolites. *Magn Reson Med* 11: 47-63, 1989
- 4) Gill SS, Thomas DGT, Bruggen NV, Gadian DG, Peden CJ, Bell JD, Cox IJ, Menon DK, Iles RA, Bryant DJ, Coutts GA: Proton MR spectroscopy of intracranial tumours: In vivo and vitro studies. *J Comput Assist Tomogr* 14: 497-504, 1990
- 5) Graham GD, Blamire AM, Howseman AM, Rothman DL, Fayad PB, Brass LM, Petroff OAC, Shulman RG, Prichard JW: Proton magnetic resonance spectroscopy of cerebral lactate and other metabolites in stroke patients. *Stroke* 23: 333-340, 1992
- 6) Hanstock CC, Boisvert DPJ, Bendall MR, Allen PS: In vivo assessment of focal brain lactate alterations with NMR proton spectroscopy. *J Cereb Blood Flow Metab* 8: 208-214, 1988
- 7) Hossman KA: The pathophysiology of experimental brain edema. *Neurosurg Rev* 12: 263-280, 1989
- 8) Houkin K, Kwee IL, Nakada T: Persistent high lactate level as a sensitive MR spectroscopy indicator of completed infarction. *J Neurosurg* 72: 763-766, 1990
- 9) Klatzo I: Neuropathological aspects of brain edema. *J Neuropath Exp Neurol* 26: 1-14, 1967
- 10) Koller KJ, Zaczek R, Coyle J: N-acetyl-aspartyl-glutamate: Regional levels in rat brain and the effects of brain lesions as determined by a new HPLC method. *J Neurochem* 43: 1136-1142, 1984
- 11) Matthews PM, Francis G, Antel J, Arnold DL: Proton magnetic resonance spectroscopy for metabolic characterization of plaques in multiple sclerosis. *Neurology* 41: 1251-1256, 1991
- 12) Miller BL: A review of chemical issues in ¹H NMR spectroscopy: N-acetyl-aspartate, creatine and choline. *NMR Biomed* 4: 47-52, 1991
- 13) Narayana PA, Johnston D, Flamig DP: In vivo proton magnetic resonance spectroscopy studies of human brain. *Magn Reson Imaging* 9: 303-308, 1991
- 14) Peeling J, Wong D, Sutherland GR: Nuclear magnetic resonance study of regional metabolism after forebrain ischemia in rats. *Stroke* 20: 633-640, 1989
- 15) Petroff OAC, Ogino T, Alger JR: High-resolution proton magnetic resonance spectroscopy of rabbit brain: Regional metabolite levels and postmortem changes. *J Neurochem* 51: 163-171, 1988
- 16) Richards TL: Proton MR spectroscopy in multiple sclerosis: Value in establishing diagnosis, monitoring progression, and evaluating therapy. *AJR* 157: 1073-1078, 1991
- 17) Tallan HH: Studies on the distribution of N-acetyl-L-aspartic acid in brain. *J Biol Chem* 224: 41-45, 1956

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