PAPER

Is NAA reduction in normal contralateral cerebral tissue in stroke patients dependent on underlying risk factors?

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Background and purpose: This retrospective study investigated the dependence of *N*-acetyl aspartate (NAA) ratios on risk factors for cerebral vasculopathy such as sex, age, hypertension, diabetes mellitus, carotid stenosis, and dyslipidaemia, which may have affected brain vessels and induced metabolic brain abnormalities prior to stroke. We hypothesise that in stroke patients metabolic alterations in the apparently normal contralateral brain are dependent on the presence or not of such risk factors.

Methods: Fifty nine patients (31 male, 28 female: 58.8 ± 16.1 years old) with cortical middle cerebral artery (MCA) territory infarction were included. Long echo time chemical shift imaging spectroscopy was carried out on a Siemens 1.5 T Magnetom Vision scanner using a multi-voxel PRESS technique. Metabolite ratios (NAA/choline, NAA/creatine, lactate/choline, etc) were studied using uni- and multivariate analyses with respect to common risk factors. The influence of age, stroke lesion size, and time since stroke was studied using a linear regression approach.

Results: Age, sex, and hypertension all appeared to individually influence metabolite ratios, although only hypertension was significant after multivariate analysis. In both basal ganglia and periventricular white matter regions in apparently normal contralateral brain, the NAA/choline ratio was significantly lower in hypertensive (1.37 ± 0.16 and 1.50 ± 0.19 , respectively) than in normotensive patients (1.72 ± 0.19 and 1.85 ± 0.15 , respectively).

Conclusions: Regarding MCA infarction, contralateral tissue remote from the lesion behaves abnormally in the presence of hypertension, the NAA ratios in hypertensive patients being significantly lower. These data suggest that hypertension may compromise the use of contralateral tissue data as a reference for comparison with ischaemic tissue.

Proton magnetic resonance spectroscopy can be used to assess abnormalities in the brain of stroke patients. A profound decrease in *N*-acetyl aspartate (NAA) and abnormal accumulation of lactate are common features of the infarcted brain. Abnormalities in the apparently unaffected contralateral brain have been less extensively studied. Many authors have considered the contralateral brain to be normal as regards metabolite concentration and it is commonplace to compare the data in the stroke area with data observed in the contralateral hemisphere distant from the acute ischaemic region.

Other studies have shown that abnormalities of the contralateral brain can be demonstrated by various techniques. Although these abnormalities may be explained by the functional consequences of stroke or by clinically silent brain ischaemia occurring concomitantly with the stroke itself, the most probable explanation is the presence of pre-existing abnormalities of the brain such as cerebral small vessel disease (CSVD) or other subtypes of cerebral microangiopathy. Chronic ischaemia is known to alter the metabolic pathways of the brain. Many studies have shown that NAA is reduced in chronic ischaemia of the brain while choline (Cho) is slightly increased, thus inducing a decrease in the NAA/Cho ratio.

The aim of the present work was to study brain tissue contralateral to stroke lesion in order to investigate the dependence of the NAA ratios on common risk factors for cerebral vasculopathy such as sex, age, hypertension, diabetes mellitus, carotid stenosis, dyslipidaemia, and smoking. These risk factors may have affected brain vessels and induced metabolic abnormalities of the brain prior to stroke onset. Thus, the hypothesis underlying the present study is that, in patients with stroke, the contralateral brain alterations are dependent on the presence or not of such risk factors.

METHODS

Study population

The study was performed using a Siemens 1.5 T Magnetom Vision scanner. Fifty nine patients (31 male, 28 female; 58.8 ± 16.1 years old) with a cortical middle cerebral artery (MCA) territory infarction were included in the study. The mean delay between stroke and magnetic resonance spectroscopy (MRS) was 19.2 ± 35.8 days (range: 2–175 days). The diagnosis was established according to clinical and radiological criteria. The clinical criteria were those outlined by the National Institute of Neurological Stroke and Disease¹: acute onset of cortical or sub-cortical functions in the MCA territory, with hemiplegia mainly affecting the brachio-facial territory and sensory deficit, hemianopia, and aphasia being more or less associated. In all cases, the neurological disorders lasted over 24 h. Patients with obvious haemorrhage or tumour seen on CT scan or MRI were excluded from the study. The study was approved by the local ethics committee. The principal patient data are summarised in table 1.

Risk factors

The principal risk factors investigated in this study were:

- hypertension, which was considered present if the patient's blood pressure was 160/95 mm Hg or higher or if the patient had received medical treatment for hypertension for at least 12 months,

Abbreviations: CSVD, cerebral small vessel disease; MCA, middle cerebral artery; MRS, magnetic resonance spectroscopy; NAA, *N*-acetyl aspartate; TG, triglycerides; TSE, turbo spin echo

- (b) diabetes mellitus was coded as present if a subject was being treated for diabetes or diabetes was indicated by fasting blood glucose measurements (>126 mg/dl),
- (c) dyslipidaemia was coded as present if a subject had elevated triglycerides ($\text{TG} > 1.5$ mmol/l) and/or low high density lipoproteins ($\text{HDL-cholesterol} < 0.5$ mmol/l),
- (d) uni- or bilateral carotid stenosis detected by carotid ultrasonography, and
- (e) tabagism.

Magnetic resonance imaging

Images acquired in the three orthogonal planes using a double echo T2 weighted turbo spin echo (TSE) sequence (TE 16/98, TR 4400) for diagnostic purposes were used for spectroscopy localisation. The stroke lesion volume was also estimated from this sequence using standard planimetry techniques.

MRS imaging

Spectra were acquired with long echo time chemical shift imaging spectroscopy (TE/TR: 270/1500 ms) using a multi-voxel PRESS technique (voxel dimensions of $10 \times 15 \times 15$ mm). Spectroscopy was performed in the transversal plane and with a slice thickness of 10 mm. In order to efficiently study the metabolic state of the basal ganglia and white matter, the spectroscopic grid was positioned so as to provide relatively uncontaminated spectra from basal ganglia and periventricular white matter (fig 1). Water suppression was achieved by applying chemical shift selective (CHESS) saturation pulses. Shimming was performed automatically using the manufacturer's programme 3DSHIM.

The CSI data were processed using the spectroscopy analysis package MRUI 99.2 (Magnetic Resonance User Interface: www.mrui.uab.es/mrui). Residual water resonance was removed using the HLSVD filter routine.² Peak detection and quantitation were performed in the time domain using a VARPRO-like algorithm called AMARES,³ which allows inclusion of a large amount of prior knowledge. The resonances quantified in each metabolite spectrum were the NAA peak at 2.02 ppm, the Cr-PCr peak (referred to as Cr in the text) at 3.02 ppm, the choline peak at 3.20 ppm, and the lactate doublet at 1.33 ppm. Peak integrals were quantified by fitting to a Gaussian line shape. In the absence of absolute quantitation, the spectroscopic data were expressed simply as ratios (for example, NAA/Cho).

Statistical analysis

Metabolite ratios (NAA/choline (Cho), NAA/creatine (Cr), Cho/Cr, lactate (Lac)/Cho, etc) were studied using uni- and multivariate analyses with respect to the common risk factors of sex, hypertension, dyslipidaemia, carotid stenosis, diabetes mellitus, and smoking. Age, stroke lesion volume, and delay between stroke and MR examination were studied using a

linear regression approach. The statistical tests were performed using the statistical package SYSTAT 7.0 for Windows (SPSS, Evanston, IL, USA). Statistical significance was accepted for $p < 0.05$.

RESULTS

The spectroscopic data were divided into two groups: those concerning the basal ganglia and those concerning the periventricular white matter. Within the cerebral hemisphere contralateral to the stroke lesion, one or two voxels were analysed from both periventricular white matter and the basal ganglia. Occasionally (7/59), the anterior portion of the basal ganglia gave low quality spectra due to poor shimming and subsequent peak overlap between Cho and Cr, and these voxels were excluded from further analysis. Thus, the data from the grey and white matter locations are mostly presented as mean values.

Table 2 summarises the results for NAA/Cho from the univariate and linear regression analyses. Results for Cho/Cr and Lac ratios are not shown as no significant differences were observed. The NAA/Cr results were similar to, but slightly less significant than, the NAA/Cho results. Univariate analysis of the data from basal ganglia showed NAA ratios to be significantly different as regards sex (NAA/Cho: (M, male) 1.45 ± 0.20 v (F, female) 1.59 ± 0.27) and the presence of hypertension (NAA/Cho: 1.37 ± 0.16 v 1.72 ± 0.16). Similarly, in periventricular white matter, the NAA ratios were found to be significantly different as regards sex (NAA/Cho: (M) 1.59 ± 0.25 v (F) 1.72 ± 0.22) and the presence of hypertension (NAA/Cho: 1.50 ± 0.19 v 1.85 ± 0.15). The linear regression analysis of NAA ratios with age also provided statistically significant (although somewhat loose) negative correlations in both of the studied territories. No statistically significant correlation was observed for the linear regression analyses of metabolite ratios with respect to the volume of the stroke lesion and the time since stroke.

Following multivariate analysis using the factors found to be significant after univariate analysis, only hypertension remained statistically significant for the NAA ratios in the territories explored. The significant difference between NAA ratios in hypertensive and non-hypertensive patients is particularly well illustrated in fig 2. Although age and sex figured in the univariate analysis, their lack of statistical significance in the multivariate analysis suggests some covariance with the presence of hypertension.

DISCUSSION

Supposedly normal contralateral tissue is common used as a reference when normal and pathological ^1H spectroscopic data are compared. However, in the context of proton spectroscopy in stroke, few studies have considered the consequences of multiple risk factors on the apparently normal contralateral hemisphere. In our investigation we have chosen to take a closer look at this largely ignored topic.

In this study, we deliberately chose long TE spectroscopic imaging as opposed to a short TE single voxel approach. Although there is an obvious loss in sensitivity at longer echo times, the spectra are much less complex and the baseline is particularly flat and devoid of most lipid macromolecules that may contaminate them. Although the use of CSI to estimate absolute metabolite concentrations is feasible, the examination takes too long when dealing with stroke patients. Despite the inconvenience of covering only a limited number of voxels, most absolute concentration measurements have been performed using a short echo time, single voxel approach. For example, Matthews *et al*⁴ used a single voxel approach to quantify metabolite concentrations within stroke lesions and the corresponding contralateral tissue. Although

Table 1 Patient data for the 59 study subjects

Criteria	Data
Sex ratio (M/F)	31/28
Age (years)	58.8 ± 16.1 (range: 30–85)
Hypertension	34/59
Diabetes mellitus	5/59
Dyslipidaemia	16/59
Carotid stenosis	6/59
Smokers	9/59
Delay between stroke and MR (days)	19.2 ± 35.8 (range: 2–175)
Stroke lesion volume (cm^3)	33.2 ± 49.5 (range: 9.3–96.2)

Figure 1 (A) Typical spectroscopic grid positioning on T2 weighted TSE sequence with ^1H spectra (TE 270 ms) emanating from (B) grey and (C) white matter voxels in the hemisphere contralateral to stroke lesion.

risk factors were not considered in their study, significantly reduced levels of Cho, Cr, and NAA were observed within the apparently normal contralateral tissue.

In the present study, the influence of factors such as sex, age, hypertension, dyslipidaemia, carotid stenosis, diabetes mellitus, lesion volume, and smoking on the supposedly normal contralateral hemisphere was investigated. Age, sex, and hypertension all appeared to contribute individually to metabolite ratios, but only hypertension maintained a significant influence after multivariate analysis.

Only a few studies (table 3) have considered the influence of risk factors on cerebral metabolites,^{3–11} and most of these have concentrated on white matter. In obstructive sleep apnoea, Kamba *et al*⁵ found that age and hypertension had significant effects on NAA/Cho ratios in cerebral white matter. In cerebral cortex, only age influenced the spectroscopic data. However, only one single voxel was chosen for each tissue type.

Hund-Georgiadis *et al*⁹ observed significantly depressed NAA/Cho and NAA/Cr ratios in patients (all hypertensive) with CSVD in a single voxel MRS study of normal appearing periventricular white matter. Capizzano *et al*¹⁰ have also shown that patients with dementia have reduced (NAA) and NAA/Cr in both cortical and white matter regions. In clinical terms, the simultaneous occurrence of minor stroke symptoms and a history of hypertension are suggestive of CSVD. Indeed, the cerebral vasculature in hypertensive patients undergoes substantial alteration, including fibrinoid degeneration of the intima and increased arterial wall thickness in the small arteries and atherosclerosis in the large vessels. In

small vessel disease, lesions caused by deep penetrating non-branching arteriole occlusion or narrowing may involve watershed areas of subcortical grey or white matter.¹² However, despite the presence of white matter lesions, studies have shown that the association between imaging criteria and CSVD remains weak.⁹

There are various explanations for the low NAA ratios found in white matter and subcortical grey matter. Positron emission tomography and single photon tomography studies have shown that subcortical grey matter might suffer from hypoperfusion in cerebral microangiopathy, a form of vascular dementia known to be related to hypertension and arteriosclerosis.¹³ It has also been shown that thrombin inhibition improves the NAA/Cr ratio in vascular dementia.¹⁴ This finding suggests that arterial thrombosis may also be involved in the pathogenesis of tissue hypoperfusion and the subsequent metabolic impairment of neurones.

MRI may underestimate neuronal loss in vascular dementia because tissue shrinkage is attenuated by gliosis. Therefore, as ^1H MR spectroscopy reveals the presence of NAA localised within the neurones, it is expected to be a more sensitive indicator of neuronal loss than tissue shrinkage.¹⁰ The clinical importance of metabolic changes in vascular dementia was stressed by Mielke *et al*,¹⁵ who found that the severity of dementia was related more to the extent of cortical hypometabolism than to the amount of tissue destruction.

Age is very important in most spectroscopic studies. Grachev *et al*,¹⁶ Angelie *et al*,¹⁸ and Kamba *et al*⁵ observed reduced NAA/Cr and NAA/Cho as a function of age.

Table 2 Metabolite ratios from univariate and linear regression analyses of common risk factors

Criteria	NAA/Cho basal ganglia	p	NAA/Cho periventricular WM	p
Gender	Male: 1.45 ± 0.20 Female: 1.59 ± 0.27	0.031	Male: 1.59 ± 0.25 Female: 1.72 ± 0.22	0.036
Hypertension	Yes: 1.37 ± 0.16 No: 1.72 ± 0.19	$<10^{-6}$	Yes: 1.50 ± 0.19 No: 1.85 ± 0.15	$<10^{-6}$
Dyslipidaemia	Yes: 1.53 ± 0.24 No: 1.51 ± 0.25	0.83 (NS)	Yes: 1.67 ± 0.26 No: 1.64 ± 0.24	0.75 (NS)
Stenosis	Yes: 1.47 ± 0.27 No: 1.52 ± 0.24	0.58 (NS)	Yes: 1.74 ± 0.22 No: 1.64 ± 0.25	0.32 (NS)
Diabetes mellitus	Yes: 1.45 ± 0.17 No: 1.52 ± 0.25	0.50 (NS)	Yes: 1.58 ± 0.24 No: 1.66 ± 0.25	0.47 (NS)
Tobacco use	Yes: 1.60 ± 0.38 No: 1.50 ± 0.21	0.23 (NS)	Yes: 1.71 ± 0.36 No: 1.64 ± 0.22	0.37 (NS)
Age	$-0.0062 \times \text{age} + 1.88$ $R^2 = 0.17$	0.0013	$-0.0058 \times \text{age} + 1.99$ $R^2 = 0.15$	0.0028

Figure 2 Comparison of NAA/Cho in basal ganglia of hypertensive and non-hypertensive patients.

In our study, a significant negative correlation was observed between the NAA ratios and age (fig 3). However, the hypertensive group was generally older than the non-hypertensive group, thereby introducing a bias. In fact, when the NAA ratio variations of hypertensive and non-hypertensive subjects were analysed independently with age, the significant negative correlation disappeared in both subgroups.

Gender has also been suggested to account for differences observed in certain studies. Wilkinson *et al*¹⁹ and Grachev *et al*^{16,17} observed small, but significant differences between males and females. However, Komoroski *et al*²⁰ and Pouwels *et al*²¹ observed no differences. Again, in our study, we observed a small difference in NAA/Cho in both the basal ganglia and the periventricular white matter as a function of sex. However, a greater proportion of the male population were hypertensive (21/31 men were hypertensive *v* 13/28 women) and older (men 62 ± 16 years old *v* women 56 ± 16 years old), thereby introducing a double bias into the analysis of the influence of sex.

No correlation was found between the NAA ratios and stroke volume measured on MRI. Thus, lesion volume had no apparent effect on the metabolic state within the relatively remote regions of grey and white matter studied. Although tissue within the hemisphere ipsilateral to the lesion, and bordering the ischaemic insult, is often affected,²² we chose to investigate the apparently normal appearing tissue in the much more remote contralateral hemisphere.

This work is a retrospective study of brain metabolism, and the delay between stroke and spectroscopy was quite variable, although most patients were seen within the first month after stroke. Despite the relatively large time window, the delay between stroke and MR examination did not reveal any significant tendency. Hence, any oedema or mass effect

Figure 3 Variation of NAA/Cho in basal ganglia as a function of age in all patients (hypertensive and non-hypertensive).

from the patients with large stroke and swelling did not influence the metabolic data from the more remote locations studied here.

The low NAA ratios in basal ganglia and white matter might also be explained by a diaschisis effect. Diaschisis results in brain dysfunction from neuronal disconnectivity and is a common occurrence after cerebral infarction.²³ Moreover, it causes a reduction in neuronal synaptic functions in other areas of the central nervous system distant from the stroke lesion. These remote effects result from deafferentation. The existence of diaschisis is most commonly accompanied by depression of cerebral blood flow extending beyond the anatomical lesion. To date, there have been few studies on diaschisis with ¹H spectroscopy. A clinical case report on crossed cerebellar diaschisis described reduced NAA in the affected cerebellar hemisphere.²⁴

In the present study, the reduction in NAA ratios is bilateral: it is predominantly ipsilateral, but is also contralateral to the lesion. Although diaschisis may play a role in the behaviour of the ipsilateral tissue, it is highly unlikely that it exerted a significant effect on the much more remote contralateral hemisphere. Moreover, the size of the stroke lesion did not appear to play a role.

Other traditional risk factors such as dyslipidaemia, carotid stenosis, diabetes mellitus, and smoking did not significantly influence the contralateral spectroscopic data. However, in our population, smoking (9/59), diabetes (5/59), and carotid stenosis (6/59) were infrequent and this may have significantly reduced the statistical power of the analysis, and perhaps, may explain the lack of statistical significance, if any.

If cerebral microangiopathy is a central issue (and hypertension, the predominant risk factor in our study would

Table 3 Previous studies on stroke risk factors and MR spectroscopy

Authors	Risk factors studied	Population	Tissue studied in spectroscopy
Kamba <i>et al</i> ^f	Hypertension Cardiac disease Diabetes mellitus Hyperlipidaemia	Sleep apnoea patients	White matter
Parsons <i>et al</i> ^f Bakker <i>et al</i> ^f	Hyperglycaemia Carotid artery occlusion	Stroke patients TIA or minor stroke patients	Ischaemic lesion White matter (CSO) ipsilateral to vessel occlusion
Firbank <i>et al</i> ^f Hund-Georgiadis <i>et al</i> ^f Capizzano <i>et al</i> ^o	White matter hyperintensities Cerebral small vessel disease Vascular dementia	Elderly volunteers Patients with cerebral small vessel disease Subcortical ischaemic vascular dementia	Normal appearing white matter Parietal white matter Cortical and white matter

suggest it is), then it is crucial to diagnose it as early as possible. MRS guided by MRI been shown to be valuable in the detection of metabolic abnormalities within apparently normal tissue. This is of paramount importance in the clinical context, as the identification of patients at risk will allow their appropriate management and treatment before the onset of stroke or other vascular related insults such as dementia.

In conclusion, this study has highlighted the need to take into account the influence of common risk factors, notably hypertension, when using presumed healthy contralateral brain tissue as a reference for comparison with ischaemic tissue.

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ELECTRONIC-DATABASE INFORMATION

The Magnetic Resonance User Interface is at www.mrui.uab.es/mrui

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