Studies of Acute Ischemic Stroke With Proton Magnetic Resonance Spectroscopy

Relation Between Time From Onset, Neurological Deficit, Metabolite Abnormalities in the Infarct, Blood Flow, and Clinical Outcome

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Background and Purpose—Proton magnetic resonance spectroscopy (MRS) can be used to study metabolite abnormalities in the brains of stroke patients. We have used it to examine the relations between the metabolites in the infarct (N-acetylaspartate [NAA] and lactate) and the time lapse from stroke to MRS, the presenting neurological deficit, infarct size and swelling (on MRI), blood flow to the infarct (estimated by transcranial Doppler ultrasound), and clinical outcome.

Methods—Patients with symptoms of a moderate to large cortical infarct underwent serial proton MRS (Siemens 1.5 Magnetom) within 4 days, from 5 to 10, and from 11 to 35 days after the stroke. A long echo time PRESS single voxel or chemical shift imaging acquisition was used. Transcranial Doppler ultrasound was performed daily in the first week and twice per week thereafter until the final MRS. Clinical features and baseline demographic data were collected independently by a stroke physician and 6-month outcome by postal questionnaire.

Results—Fifty patients underwent at least 1 MRS examination. Reduced NAA in the infarct within the first 4 days was related to the clinical stroke syndrome, more extensive infarction, more severely reduced blood supply to the infarct, and the presence of lactate. The presence of lactate was related to large infarcts and reduced NAA. Swelling in the infarct was most closely associated with large infarcts and reduced blood supply but not reduced NAA or the presence of lactate. Clinical outcome was most closely related to the extent of the infarct (more than to the clinical syndrome)—the larger the infarct the worse the outcome—but not to the metabolite concentrations alone.

Conclusions—The reduction in NAA (but not the presence of lactate) in a visible infarct was related to the reduction in blood flow to the infarct, which in turn was related to infarct extent and clinical outcome. (Stroke. 1998;29:1618-1624.)

Key Words: cerebral infarct ■ lactate ■ magnetic resonance imaging ■ middle cerebral artery ■ N-acetylaspartate ■ spectroscopy, nuclear magnetic resonance ■ stroke ■ ultrasound, Doppler, transcranial

Stroke is a common cause of death and the most common cause of disability in adults.1 As yet there is no really effective acute treatment, although aspirin is of marginal benefit.2 Pathophysiological studies in animal models are helpful,3 but there is a need to improve understanding of human stroke because this might improve the design of clinical trials for new therapeutic agents. For example, the exact time course of neuronal death after interruption of the arterial blood supply to part of the brain varies, and there is evidence that it may take up to several days for all the neurons to die.4,5 Whether the brain might be salvageable before this is uncertain,6 but better definition of the natural history of the brain lesion, and possible markers of neuronal viability, would be useful.

MRI and MRS provide assessment of neuronal viability. The presence of lactate is thought to indicate ischemia (anaerobic metabolism) and reduced N acetylaspartate (NAA) to indicate a reduction in the number of viable neurons.7 Several studies have reported observations of acute stroke patients at various time points with MRS.8–17 Reduced NAA in the visible area of infarction is a consistent finding from very early after the stroke (within 2 hours is the earliest reported).14 The findings for choline and creatine (detected with proton MRS) vary. Lactate is detected early (attributed to neuronal ischemia before infarction), then disappears to reappear at approximately 3 weeks (attributed to inflammatory cell infiltrate).10 There is little information on the relation between these findings and infarct size, blood flow, the clinical presentation, or outcome. Saunders et al14 examined 26 patients within 72 hours of the stroke and found that mean infarct NAA was higher in those who were independent at 6 months than in those who were dead or dependent but did not examine the interaction with other baseline variables. Federico et al15

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studied 14 patients within 1 week of the stroke and found a positive correlation between reduced NAA and severe neurological deficit at follow-up as assessed by the Scandinavian Stroke Score. Kugel et al, using MRS and positron emission tomography (PET) to measure cerebral blood flow, found reduced NAA in areas of reduced perfusion in 4 patients, though in 2 patients NAA was reduced in an area with apparently persistent blood flow. Graham et al correlated infarct volume with metabolites, neurological deficit, clinical outcome, and relative cerebral blood flow measured by single photon emission computed tomography (SPECT) in 32 patients examined with MRS up to 19 days after the stroke and found significant associations between the presence or absence of lactate, reduced NAA, blood flow, and outcome. However, because all of these studies were small and examined patients at a range of times after the stroke, the results are likely to be influenced by the case mix of strokes included and the scan timing and are therefore difficult to extrapolate to the generality of stroke patients. We hypothesized that (a) patients with markedly reduced blood flow in the middle cerebral artery (MCA) would have symptoms of extensive infarction, big infarcts, reduced NAA, and perhaps more lactate compared with patients with less abnormal MCA flow; (b) that therefore blood velocity reduction, or NAA reduction, or the presence of lactate soon after the stroke might distinguish those with a bad outcome from good; and (c) that infarct swelling might be proportional to the degree of reduction in blood flow or NAA or the presence of lactate as well as infarct size.

Subjects and Methods

The study took place between June 1994 and February 1997 in a large city teaching hospital without a casualty department but with a stroke unit.

Patient Selection

All patients admitted to our hospital were examined by a stroke physician, and the clinical syndrome was classified according to the Oxfordshire Community Stroke Project (OCSP) into a partial or total anterior circulation stroke (PACS or TACS) corresponding to infarction in the anterior cerebral artery (ACA) and without water suppression to enable a first-order phase correction for the effects of eddy currents and field inhomogeneities. Data processing was performed on a Sun SPARC 20 with software written in C and consisted of: voxel shifting of the VOI position, 2-dimensional spatial fast Fourier transforms, phase correction of the water-suppressed signals with the use of the water reference signal, residual water removal, and a fast Fourier transform of the time domain data to give spectra. Areas under the spectrum corresponding to the concentration of the metabolites were calculated as for the single voxel method. A map of each metabolite was then made by bilinear interpolation of the areas under the relevant peaks calculated from the spectrum from each voxel. Normalization procedures were then implemented to correct for the in-slice variation. For anatomic comparisons in patients, the color spectroscopic image map was superimposed on the gray-scale T2-weighted image of the brain.

The blood flow to the infarct was estimated with the use of transcranial Doppler (TCD) ultrasound. We used either an EME TC 2020 Pioneer or an Acuson 128xp 10v, both functioning with 2 MHz probes and TCD software. The middle, anterior, and posterior cerebral arteries (MCA, ACA, and PICA, respectively) on both sides were examined through the temporal bone windows. The peak systolic and mean velocities and pulsatility index were noted in each artery. The examinations were performed as soon as possible after admission, daily in the first week and twice in the subsequent 2
Follow-up

The patients were followed up at 6 months with the modified Rankin scale (0 indicating no symptoms and 6 dead). Follow-up was by telephone or postal questionnaire by trained staff who were blind to the imaging results.

Statistical Analysis

The clinical, MRI, MRS, and TCD data were entered into a Dbase4 database and analyzed with SPSS/PC+ (Statistics Package for the Social Sciences, SPSS UK, SPSS House). The TCD results were simplified to take account of individual patient variation and the effect of age by expressing the velocity in the symptomatic artery (usually the middle cerebral) as a proportion of the velocity in the asymptomatic contralateral artery: no detected flow in the symptomatic artery was coded as 0; velocity reduced to less than half of the asymptomatic side, 1; reduced but to no worse than approximately half the asymptomatic side, 2; the same as the asymptomatic side, 3; and greater than the asymptomatic side, 4. The MRS results were coded in a similarly simple manner: lactate (present or absent); NAA as a proportion of the NAA in the contralateral normal brain or remote and normal-appearing part of the ipsilateral hemisphere. For some of the analyses, the NAA was categorized as less than or greater than half of the value of that in the normal area. The possible associations between neurological deficit, infarct size and swelling, metabolite levels, and blood velocity were tested for with the use of $\chi^2$ tests, nonparametric tests (Mann-Whitney $U$ test), and logistic regression.

Ethics

The study was approved by the local Ethics of Medical Research Committee.

Results

During the study period approximately 500 stroke patients were admitted to the hospital, but many were unsuitable because they either had the wrong sort of stroke (too mild, lacunar, or posterior fossa), were admitted too late after their stroke, were too ill to go into the MR scanner safely, refused to take part in the study, recovered or died too quickly, had no bone window for TCD, or were found to have a hemorrhage as the cause of their stroke. In addition, there were scanner service days, breakdowns, and clinical demand that precluded inclusion of patients even when a suitable one was available. Approximately 200 potentially eligible patients were admitted with the right sort of clinical features during the time of the study, of whom we were able to do spectroscopy in 50. There were 36 TACI (72%), 10 PACI (20%), and 4 POCI (8%). One patient initially classified as having a cortical stroke was given an eventual clinical diagnosis of lacunar (8%). One patient initially classified as having a cortical infarct, although a cortical infarct was found on the MR. The stroke was given an eventual clinical diagnosis of lacunar, or posterior fossa), were admitted too late after their stroke, were too ill to go into the MR scanner safely, refused to take part in the study, recovered or died too quickly, had no bone window for TCD, or were found to have a hemorrhage as the cause of their stroke. In addition, there were scanner service days, breakdowns, and clinical demand that precluded inclusion of patients even when a suitable one was available. Approximately 200 potentially eligible patients were admitted with the right sort of clinical features during the time of the study, of whom we were able to do spectroscopy in 50. There were 36 TACI (72%), 10 PACI (20%), and 4 POCI (8%). One patient initially classified as having a cortical stroke was given an eventual clinical diagnosis of lacunar infarct, although a cortical infarct was found on the MR. The mean age was 66 years, range 26 to 90 years. Fourteen (28%) were dead at 6 months. Thirty-seven (74%) patients were dead or dependent (Rankin 3 to 6) at 6 months, and 13 (26%) were independent, with this relatively poor outcome reflecting the severity of the strokes included.

The earliest MR scans were done at 12 hours after the onset of the stroke and the latest at 31 days (median 3 days). Fifty had at least 1 out of 3 MRS studies, of whom 43 were scanned within 4 days, 31 between 5 and 10 days, and 13 after 10 days from stroke onset. Failure to scan all subjects serially was due to the death of the patient, the patients being too ill to maintain an airway, being discharged home or back to their referring hospital, or lack of available time on the MR scanner (main problem). The second MRS was done at a median of 7 days and the third at a median of 12 days. However, the MRS was only successful in yielding metabolite results in 22 patients who only had 1 scan, 11 patients who had 2 sequential scans, and 7 patients who had 3 sequential scans (Table 1). Failure to obtain metabolite results was mainly due to the patient being unable to tolerate the lengthy scanning time (1 hour) and not to technical factors such as poor signal-to-noise ratios.

We observed a wide range of NAA values in the infarct with respect to the normal hemisphere from normal to absent in patients scanned within the first 4 days (Figure 1). In patients with successful sequential scans, the NAA value fell in 5, remained the same in 8, and appeared to increase in 5 patients between the initial and the follow-up MRS. In a univariate analysis, reduction in the concentration of NAA in the infarct within 4 days of the stroke (to less than half the value or worse of normal brain) was associated with large infarcts ($P<0.01$) but not the timing of the scan, reduction in blood velocity to the infarct, infarct swelling (on the initial or later scan between 5 and 10 days), or the presence of lactate. In a multiple logistic regression, however, reduction in NAA was weakly associated with the clinical stroke syndrome ($P=0.08$) and the degree of reduction in blood velocity to the infarct ($P=0.06$) and was significantly associated with the extent of the infarct ($P=0.03$) and the presence of lactate ($P=0.04$) but not the timing of the scan or the amount of swelling in the infarct (Table 2).

Lactate was detected in 28 MRS examinations and was either not detected or there were lipid contaminants (either from cell membrane breakdown products in the infarct or bone marrow scalp contaminants) in 39. Lactate was found more often at earlier than at later examinations (Figure 2). The MRS examinations in which lactate was detected (median 3 days, 95% confidence intervals [CI] 2 to 5 days) were done significantly sooner after the stroke than those in which lactate was not detected (median 5 days, 95% CI 4 to 8 days): difference between the medians = 1 day, 95% CI 0 to 4 days.

| TABLE 1. Timing of MRS Examinations That Were Successful in Yielding Metabolites (NAA, With or Without Lactate) |
|---|---|
| MRS Examinations and Timing | No. of Successful Examinations |
| All patients who had S1 | 17 |
| All patients who had S2 | 3 |
| All patients who had S3 | 2 |
| Patients who had S1 and S2 only | 10 |
| Patients who had S2 and S3 only | 1 |
| Patients who had S1 and S3 only | 0 |
| All patients who had all 3 MRS examinations | 7 |

S1 indicates MRS at 0 to 4 days; S2, MRS at 5 to 10 days, and S3, MRS at 11 to 20 days.
In a univariate analysis, the presence of lactate in the infarct within the first 4 days of the stroke was associated with extensive infarction ($P<0.02$) but not with the amount of swelling in the infarct (within 4 days), the degree of reduction in the blood velocity to the infarct, the clinical stroke syndrome, or the reduction in NAA. The presence of lactate within 4 days of the stroke was also not associated with subsequent infarct swelling on brain imaging at 5 to 10 days. From multiple logistic regression, lactate detected within 4 days of the stroke was significantly associated with large infarcts ($P<0.05$) and reduced NAA ($P=0.04$) but not the clinical stroke syndrome, timing of the scan, blood velocity, or the amount of infarct swelling (Table 2).

The mean ($\pm$SD) choline values in the infarct and contralateral normal brain were 507 ($\pm$253) and 706 ($\pm$216), respectively, and likewise the mean creatine ($\pm$SD) values were 140 ($\pm$279) and 660 ($\pm$211), respectively. The reduction in choline and creatine between infarcted and normal brain was highly significant ($P<0.0001$), though relatively speaking the infarct choline was not as markedly reduced as the infarct creatine or NAA with respect to normal brain.

Massive infarct swelling between 5 and 10 days after the stroke was weakly associated with reduced blood velocity to the infarct ($P=0.07$) and large infarcts ($P=0.08$) but not the presence of lactate (on the scan within 4 days of the infarct or later) or the degree of reduction in NAA (on initial and subsequent scans). However, the number of patients available for this analysis was very small.

In a univariate analysis, poor clinical outcome at 6 months (Rankin score 3 to 6) was significantly related to the clinical stroke syndrome ($P=0.03$), the extent of the infarct, that is, the presence of lactate ($P=0.02$), the extent of the infarct, and reduced NAA ($P=0.02$) with poor outcome at 6 months (defined as dead or dependent, ie, Rankin score 3 to 6).

**TABLE 2.** Multivariate Analysis of Factors That Might Be Associated With Presence of Lactate and Marked Reduction in NAA in Infarcts Investigated With Proton MRS Within 4 Days of Onset of Stroke Symptoms and With Poor Outcome at 6 Months (Defined as Dead or Dependent, ie, Rankin Score 3 to 6)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reduction in NAA in Infarct to $&lt;1/2$ of Normal</th>
<th>Lactate Present in Infarct</th>
<th>Dead or Dependent at 6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio 95% CI $P$</td>
<td>Odds Ratio 95% CI $P$</td>
<td>Odds Ratio 95% CI $P$</td>
</tr>
<tr>
<td>Clinical syndrome</td>
<td>4.6 3.6 $0.08$</td>
<td>0.04 $-1$, 1.8 NS</td>
<td>1.6 0.5, 2.7 NS</td>
</tr>
<tr>
<td>Reduced blood velocity</td>
<td>17.1 14.2, 20 $0.05$</td>
<td>0.2 $-2.2$, 2.6 NS</td>
<td>2.3 $-0.8$, 5.4 NS</td>
</tr>
<tr>
<td>Large infarct on T2-weighted MRI</td>
<td>0.03 $-3.3$, 3.4 $0.03$</td>
<td>13.5 11, 18.5 $0.05$</td>
<td>19 16.1, 21.9 0.04</td>
</tr>
<tr>
<td>Massive infarct swelling $&lt;4$ days</td>
<td>3.2 $-0.5$, 6.9 NS</td>
<td>0.3 $-2.2$, 2.8 NS</td>
<td>0.2 $-3.1$, 3.5 NS</td>
</tr>
<tr>
<td>Lactate present</td>
<td>44.8 41, 48 $0.04$</td>
<td>* * *</td>
<td>0.8 $-1.6$, 3.2 NS</td>
</tr>
<tr>
<td>Reduced NAA</td>
<td>* * *</td>
<td>23.4 20.5, 26 $0.04$</td>
<td>0.4 $-2.3$, 3.1 NS</td>
</tr>
</tbody>
</table>

*Not relevant.
the more extensive the infarct, the worse the clinical outcome \((P < 0.01)\), but not to the degree of reduction in NAA, the amount of swelling in the infarct, blood velocity, or the presence of lactate. On multivariate analysis, 6-month poor outcome was significantly related to large infarcts \((P = 0.04)\) but not the clinical syndrome, lactate, NAA, infarct swelling, or reduced blood velocity within the first 4 days (Table 2).

**Discussion**

We have demonstrated, using fairly simple criteria, that large cerebral infarcts are associated with reduced NAA in the infarct, the presence of lactate, reduced blood velocity, and a poor clinical outcome at 6 months but not with the amount of edema in the infarct. Even in this small series, though larger than any previous human stroke spectroscopy series, there are important variations in the severity of the stroke and other baseline variables that have an influence on long-term outcome and presumably other sequelae of the stroke.

We have classified the metabolite, blood velocity, infarct extent, and swelling results into broad categories for the analyses because too many subdivisions would reduce the statistical power of this already small sample. We used 2 MRS techniques in the study that vary in their precision (the single voxel technique is approximately twice as precise as the CSI method) but used the ratio of metabolite in the infarct to that in normal brain to circumvent this problem. The use of broad categories should also help reduce apparent changes in NAA in the infarct caused by change in its water content as edema develops during the first few days after the stroke and then resolves. The use of the ratio of NAA in the infarct to normal brain should also help reduce such effects.

We also recognize that it is difficult if not impossible to perform MRS with any great degree of success in ill stroke patients because it is difficult to ensure that they remain still, as evidenced by the number of unsuccessful MRS examinations and the number of patients in whom we were unable to repeat the MRS because they had died. The examination with nonechoplanar MR takes approximately 45 minutes (which many do not tolerate well), and even in healthy, cooperative volunteers, the reproducibility of MRS metabolite concentrations is only fair. Despite all this, the present series is one of the larger ones and one of the few that has attempted to explain changes in NAA and lactate concentrations in relation to the stroke pathophysiology.

Several studies have documented reduced NAA in the infarct,\(^8\)–\(^13\) including a further decline on repeat MRS over the first few weeks,\(^13\) which has been interpreted as indicating continuing ischemic damage, although the precise explana-

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*Figure 2.* Time course of lactate detected in the infarct over 4 weeks after stroke (some patients were scanned more than once). “Lipid” refers to either lipid contaminants from the skull or from cell membrane breakdown products in infarct. Lipid usually obscures lactate peak.

*Figure 3.* Example of T2-weighted axial MR images and single voxel proton MR spectra obtained from a patient with left MCA territory infarct. Images in a and b were obtained on day 2 and c and d on day 7 after the stroke. a and c are from normal hemisphere and b and d from infarct. Note presence of lactate (inverted peak arrowed) with relatively preserved NAA (arrowhead) on day 2. On day 7 there is no longer any lactate detected and NAA peak is smaller (arrowhead), indicating further loss of neurons.
Kugel et al. examined the relation between NAA decrease in the infarct and blood flow measured by PET in 4 patients and found that the area of NAA decrease corresponded well with the area of reduced cerebral blood flow but did not quantify the relation, nor did they examine the relation with lactate. Graham et al. examined 32 patients with MRS and 16 also with SPECT to assess blood flow and found significant associations between both the presence of lactate and NAA reduction, stroke lesion volume, and functional outcome at hospital discharge. The presence of lactate was also associated with the severity of the stroke and the reduction in blood flow on SPECT. Note, however, that in 3 of the 16 who had SPECT, the SPECT examination was done several days after the MRS. Because arterial patency is known to change after stroke (some spontaneously recanalize, others have progressive or persistent arterial occlusion), one can only really use a blood flow assessment before the MRS to infer a causal relation. The MRS examinations were also done up to 19 days after the stroke (mean 5 days) at a stage too late for early prediction of outcome. Outcome was assessed at hospital discharge, which ranged from 4 to 35 days, rather than at 6 months, when clinical recovery has stabilized. Fazekas et al. studied 18 patients with acute stroke scanned within 48 hours of the onset of the stroke and found lower NAA and the largest amounts of lactate in patients with the most severe clinical deficits and the largest perfusion defects on SPECT, but there was no clear relation between the metabolic and perfusion findings. These studies did not take account of the interplay between factors that essentially mark the same process. Thus in this study, although we found associations between metabolites and lesion size, reduced blood velocity, and the clinical syndrome, even with multivariate analysis it was difficult to identify truly independent covariates when all are likely to be so closely interrelated.

No studies in patients have looked previously at the relations between metabolite abnormalities, infarct edema, and blood flow changes. We have not found any clear relations between metabolite abnormalities (reduced NAA or the presence of lactate) and the amount of infarct edema within 4 days or between 5 and 10 days of the stroke. Interestingly, the present findings agree with earlier work by Hossman and Schuerer in a cat cerebral infarct model. They found that the animals with the most pronounced and sustained reductions in regional cerebral blood flow developed the largest infarcts but that the amount of edema in the infarct varied between animals, and there was no clear relation between the edema and the amount of lactate that could be detected in the infarct.

The explanation for our observation of the apparent increase in NAA concentration (in the infarct relative to normal brain) in several patients on their second MRS examination is probably artifactual. In 2 patients the increase was absolutely trivial, but in 3 the increase was ≥50%. All were single voxel (not CSI) measurements and all had large infarcts. It may simply reflect the high coefficient of variation in the measure of NAA with proton MRS. All 3 subjects had a third MRS that showed a return toward the NAA ratio (infarct: contralateral brain) of the initial MRS. The NAA peaks in the second MRS were all broad, which could result in errors of quantifying the peak, in turn exaggerated by using the ratio. It could be due to slight differences in positioning of the region of interest between studies, though we were very careful to ensure consistent and accurate voxel positioning. It could be due to real changes in the stroke (such as changes in the water content of the infarct), though this latter seems unlikely, or possibly due to changes in T1 and T2 values influencing the measured NAA (though this is thought unlikely to occur).

We only detected lactate in 28 of 67 scans, though in some cases it may have been present but obscured by lipid contaminants from the skull and subcutaneous tissues or from cell membrane breakdown products within the infarcted brain. Both the single voxel and CSI sequences demonstrate lactate reliably in test phantoms, so we know that the sequences work, but in patients there are numerous sources of lipid contamination or degradation of the spectra for other reasons that impair resolution of the lactate part of the spectrum. Lactate editing sequences are currently under investigation to discern lactate from lipids. The choline and creatine values were reduced in the infarct, as has been found previously, the creatine more so than choline.

Finally, all the studies reporting spectroscopic findings in stroke published so far are small. Before this report, the largest study with proton MRS concerned 32 patients, reflecting the fact that such studies are difficult to do—the technology is complex, the patients are very ill and may not tolerate the whole examination, and access to equipment may be limited. Thus any extrapolation from these small studies, with their highly selected patients and inherent bias (including this one), to the generality of stroke patients should be performed with caution, particularly in light of the fact that the reproducibility of MRS may not be as good as assumed by earlier optimistic views. As with all new techniques, an initial period of enthusiasm should be tempered by realization of the limitations, drawbacks, and impracticalities but help to focus on the true utility. Now that the technique is better quantified, studies with proton MRS should be encouraged because they present a valuable opportunity for the assessment of human stroke pathophysiology and the influence of new treatments.

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References


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