Long-term Follow-up of Cerebral Infarction Patients With Proton Magnetic Resonance Spectroscopy

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Background and Purpose With proton magnetic resonance spectroscopy it is possible to measure the content of various brain metabolites in vivo, including N-acetylaspartate (which may be used as a neuronal marker), creatine, choline, and lactate. The content of these brain metabolites was measured serially from the acute stage to the chronic stage of infarction. Regional cerebral blood flow was also measured within the affected areas. These factors were compared with the clinical outcome.

Methods Six patients with ischemic stroke were examined serially from the acute stage (≤2 days) to the chronic stage (>6 months) with proton magnetic resonance spectroscopy. Cerebral blood flow was measured with single-photon emission-computed tomography with Tc-labeled <i>l</i>-hexamethylpropyleneamine oxime as flow tracer.

Results Lactate was found in all patients in the acute stage of stroke. Lactate was also found in the 3 largest lesions in the chronic stage; in 2 of these patients lactate was not found in the subacute stage. Reduced levels of N-acetylaspartate were found in 5 patients; in the sixth patient with a small lesion no reduction was found. In all lesions reduced blood flow was found in the acute and chronic stage, whereas hyperemia was found in 4 patients in the subacute stage.

Conclusions In this preliminary study no clear correlation was found between the level of N-acetylaspartate or lactate in the acute stage of stroke and the clinical outcome; however, there does appear to be some connection between the reduction of cerebral blood flow and the spectroscopic findings in the chronic stage and to some extent the clinical outcome. Studies of larger clinical groups will be necessary to further elucidate the prognostic potential of proton magnetic resonance spectroscopy in human stroke. (Stroke. 1994;25:967-973.)

Key Words • cerebral blood flow • cerebral infarction • metabolism • spectroscopy, nuclear magnetic resonance • stroke assessment
were calculated at $TE=270$ milliseconds: NAA to choline, the calculated metabolite concentrations and ratios in the patients were compared with the values obtained from the relevant brain regions in healthy volunteers of the relevant age groups, which were recently reported in a study from our laboratory using the same method and parameters as in the present study. The metabolite resonance peaks were assigned as described by Michaelis et al.

### Regional Cerebral Blood Flow Measurements

The rCBF was measured with a Tomomatic 232 (Medimatic a/s) brain-dedicated SPECT camera. We used $500\,\text{MBq}$ Tc-labeled 1,2-hexamethylenepropyleneamine oxime ($^{99m}\text{Tc-HMPAO}$) injected intravenously as flow tracer. Linearization correction for back-diffusion was performed, and the relative rCBF within the VOI was calculated as a percentage using the contralateral symmetrically located region as reference. The rCBF measurement in the acute and subacute stages was performed within 24 hours before or after the MRS examination; in the chronic stage rCBF was measured within 1 month before or after the MRS examination.

#### Results

The patients included in the study are listed in Table 1, which also shows the area and size of the infarctions. Three infarctions were large (>4 cm in diameter) middle cerebral artery (MCA) infarctions, 2 were medium-sized (2 to 4 cm in diameter) cortical infarctions in the parietal part of the MCA area and the occipital visual cortex, and 1 was a small (<2 cm in diameter) infarction in the putamen including parts of the internal and external capsule. The clinical data regarding the initial symptoms and findings and the findings after approximately 1 year are briefly listed in Table 1. The time of examination after the onset of symptoms is listed in Table 2. The calculated metabolite ratios at $TE=270$ milliseconds and the calculated metabolite concentrations are also shown in Table 2. A spectrum at $TE=270$ milliseconds obtained from a healthy volunteer is shown in Fig 1.

The results of the measurements of the relative rCBF in the affected areas are listed in Table 2. In all patients the relative rCBF in the affected area was low in the acute stage, and in 4 patients hyperemia was found 1 week to 1 month after the onset of symptoms. The relative rCBF in the chronic stage after 7 to 17 months was similar to that in the acute stage.

In all 6 patients lactate was found within the lesions in the acute stage. In patient 1 lactate was not found in the lesion at the examinations performed 4 days and 12 days...
after the stroke, but lactate reappeared after 15 months. In patient 3 a similar pattern was seen, with lactate reappearing at the examination 7 months after stroke (Fig 2). In patient 2 lactate was present at all three examinations (Fig 3). In patients 4, 5, and 6 lactate disappeared between 1 week and 1 month after the onset of symptoms, and no lactate was found at the later examinations (Fig 3). In patients 4, 5, and 6 lactate reappeared after 15 months.

The calculated NAA concentration in the affected areas was significantly reduced (lower than the 95% confidence interval for healthy control subjects) in 5 of the patients at the examination in the chronic stage and in 4 of the patients at all examinations. In patient 6 with a small lesion the calculated NAA concentration was within the normal range at all examinations. The ratios of NAA to the cholines were reduced almost parallel with the reduction of the calculated NAA concentrations, whereas the ratios of NAA to total creatine were less sensitive as a marker of NAA loss. The calculated total creatine concentration was reduced in patients 2 and 3 at all examinations and in patients 1 and 4 at one examination. The calculated choline concentration was within the normal range at all examinations, except at one examination of patient 3. The ratio of cholines to total creatine was increased in patient 2 after 6 days but was normal at all other examinations. The calculated T₁ and T₂ relaxation times of NAA, total creatine, and cholines remained within the normal range for healthy volunteers from the acute stage to the chronic stage of stroke, whereas the calculated T₁ relaxation time of water was significantly longer in the chronic stage (P<.05), having increased from a mean±SD of...
111±16 milliseconds in the acute stage to 264±122 milliseconds in the chronic stage of stroke.

Discussion

In the acute stage we found lactate in all 6 patients, in accordance with previously reported studies of patients with acute stroke.1-5,9-11,13 In 5 of the patients the lactate content decreased to undetectable levels after 1 to 4 weeks, as also reported previously.9 However, in the 3 patients with large infarcts lactate was detected in the chronic stage between 7 and 15 months after the stroke incident, and in 2 of these patients lactate had surprisingly reappeared within the lesions. Several previous studies have reported findings of lactate in the chronic stage of brain infarction as late as 23 months after stroke.1,5,7,8,12 In a recent study Felber et al.13 using a

Fig 2. T2-weighted images (repetition time [TR], 2500 milliseconds; echo time [TE], 90 milliseconds) of patient 2 examined after 44 hours (top left), 6 days (top right), and 1 year (bottom left). The corresponding proton spectra (TR, 1500 milliseconds; TE, 270 milliseconds) are also shown (bottom right). There is continued presence of a small lactate peak at 1.3 ppm after 1 year, whereas N-acetylaspartate at 2.0 ppm, total creatine at 3.0 ppm, and the choline at 3.2 ppm are absent.
similar technique, did not find lactate in any of 8 patients with chronic infarction studied between 8 months and 6 years after onset. A time course of lactate such as we found in 2 patients, with normalization followed by an increase in the chronic stage, has not previously been reported. Presence of lactate in the acute stage of brain infarction probably reflects the degree of ischemia, whereas presence of lactate in the subacute/subchronic stage despite reperfusion hyperemia suggests continuing lactate production. Recently Rothman et al demonstrated continued lactate production in a 32-day-old infarction using MR spectroscopy. However, in a recent animal study no lactate was produced in the subacute stage of infarction. In the chronic stage of infarction lactate may be produced by inflammatory and phagocytic cells that metabolize glucose mainly to lactate even under normoxic conditions. Relative hypoperfusion (between 38% and 86%) in the affected areas was found in 5 of the 6 patients in the chronic stage. Although substantial loss of brain tissue in the affected area has probably occurred, which could explain the reduced blood flow, areas of relative ischemia could perhaps exist where anaerobic glycolysis and thus continued lactate production could take place; however, this is unlikely. Thus, the explanation for a biphasic time course of lactate found in 2 patients is not clear. In the 3 patients with smaller infarctions no lactate was found after 13 to 17 months, and in these patients the relative rCBF was not reduced to the same degree as in the 3 patients with large infarctions. This may in part be due to partial volume effects. Recently Hugg et al, using both proton and phosphorous MRS, found alkalosis in chronic infarctions despite the presence of lactate. They suggested
that one explanation may be that tissue alkalinosis stimulates glycolysis, leading to increased tissue lactate levels, because phosphofructokinase has a high pH optimum. Among several possible explanations of tissue alkalinosis Hugg et al mention "luxury perfusion"; however, we did not find elevated rCBF within the affected areas in any of our patients in the chronic stage. We did find relative hyperemia in 4 patients in the subacute stage between 7 and 30 days after the stroke, but as reported recently the method used for determination of rCBF in the present study may give rise to 10% to 30% overestimation of rCBF in the late subacute stage of stroke after day 10.26

The content of NAA was reduced markedly in the large MCA infarctions in the chronic stage and to a lesser extent in the smaller cortical infarctions, whereas no reduction was found in the small subcortical infarction after 16 months. Because NAA is almost exclusively located in neurons,14,15 it would seem that the loss of neurons is largest in large infarctions. However, given the size of the VOI used, partial volume effects may be unavoidable and may conceal metabolite changes in small lesions, thus probably in part explaining the finding of normal NAA content in patient 6 despite pronounced neurological deficits. The ratio of NAA to the choline content seems a little less sensitive for measurement of reductions in NAA than the semiquantitative estimation of the metabolite concentrations, and the ratio of NAA to total creatine is even less sensitive. This is due to almost parallel reduction in the NAA and total creatine content and only marginal reduction in the choline content within the infarctions.1,4,10 The assumption of a brain water content of 75% may result in underestimation of the metabolite concentrations because of edema, which may increase the brain water content in the lesions 1 to 2 weeks after stroke by approximately 5% to 10%.10 We found no significant changes in the relaxation behavior of NAA, total creatine, or cholines during the course of infarction compared with healthy volunteers.19,22,27 We did find increased T2 relaxation values of brain water in the lesions in the chronic stage, perhaps signifying an altered binding of brain water in the chronic stage. Sappey-Marinier et al7 in a recent study reported increased T2 relaxation times of total creatine in chronic infarction; however, they reported T1 relaxation times for NAA, total creatine, and cholines that were somewhat shorter than those previously reported.15,22,27

The present study group of 6 patients is too small to draw definite conclusions regarding the prognostic information contained in a spectroscopic examination performed in the acute stage of infarction. Graham et al8 suggested that patients with large and persistent elevations in cerebral lactate had significant neurological impairment and residual disability, whereas patients with lesser changes had a more benign clinical course. In a recent preliminary study they report significant correlation between the initial lactate and NAA concentrations and the clinical outcome.19-22 However, it should be emphasized that the lactate levels within an infarcted area depend on a variety of complex factors, such as rCBF, reperfusion, pH, and glucose level, and correlating outcome with the initial lactate content may therefore be an oversimplification. Ford et al6 in a small number of serially studied stroke patients, reported that the patients with the best recoveries had relatively preserved NAA, total creatine, and choline peaks. In the present study there does not appear to be any clear correlation between the spectroscopic findings in the acute stage of stroke and the clinical outcome. However, there does seem to be some connection between the NAA concentration measured in the chronic stage in the 3 patients with large infarctions and the relative rCBF within the lesions and to some degree with the clinical outcome. In the smaller lesions where partial volume effects may conceivably play a role, the picture is less clear. To draw more firm conclusions further studies of larger clinical groups will be necessary.

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