Magnetic Resonance Imaging and Spectroscopy: A Unique Approach to Ischemic Cerebrovascular Disease

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Introduction

During the past decades management of ischemic cerebrovascular disease was primarily directed to the prevention of stroke, rather than to the treatment of acute infarction. Today it is generally accepted that structural damage does not occur immediately and neurons may recover if therapy begins soon after onset of ischemia. Experimentally, infarction size may be reduced with restored (i.e., fibrinolysis) or improved (pharmacologic) cerebral blood flow, by increase of cellular tolerance to ischemia (i.e., hypothermia), or by prevention of secondary damage (i.e., Ca^{2+} antagonists) [22].

The development of appropriate regimens, to take advantage of the "therapeutic window" [19] in humans, necessitates diagnosis of cerebral morphology, macro-/microcirculation, and regional metabolism within a few hours of onset of clinical symptoms. Computed tomography (CT) is inadequate to demonstrate acute ischemic morphologic changes in up to 50% of cases within the first 48 h [1,23], and X-ray angiography holds the risk of side effects [31]. Metabolic assessment by positron emission tomography (PET) is presently restricted to a few centers. On the other hand, magnetic resonance (MR) is becoming more generally available and the purpose of this review is to evaluate the potential role of MR imaging (MRI). MR angiography, and MR spectroscopy as unique procedures in diagnosis of cerebral ischemia.

Patients and Methods

For this study, 180 patients who underwent MR examination because of cerebrovascular disease between August 1988 and December 1989, were retrospectively evaluated and divided into three groups.

Group I consisted of 50 patients suffering from acute ischemic neurologic deficit who were subjected to MRI within 8 h.

Group II (subacute) consisted of 70 patients with territorial stroke on whom MRI was performed between days 2 and 21 after onset of symptoms.

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Group III consisted of 60 patients with chronic cerebrovascular disease and multiple ischemic lesions.

All patients were examined on a 1.5-T magnetom (Siemens) using a circular polarized head coil (field of view/FOV = 21–25 cm), and underwent a standardized examination protocol of T1 (TR = 500 ms, TE = 15 ms) and proton density/T2 (TR = 2400 ms, TE = 15/90 ms) weighted spin-echo sequences in orthogonal orientations. Intravenous paramagnetic contrast agent (Gd-DTPA, Magnevist,) was administered in 16 patients.

An additional flow-compensated 3D fast fourier transform (FFT) gradient echo (FISP) sequence (MR angiography) of the intra- and/or extracranial arteries was performed on 130 patients (groups I-III), which immediately followed the routine protocol. The 3D-FISP sequence was adjusted to optimize the contrast between stationary tissues and flowing blood (TR = 40 ms, TE = 7 ms, flip angle 15°–25°), 64 contiguous 1–1.2 mm thick slices were acquired within 10 min. The individual images were then postprocessed by a ray-tracer algorithm to calculate projectional angiograms [2,14,25,30].

In group III, 25 patients underwent a nearly isotropic 3D-FFT gradient echo sequence (FLASH) volume study after routine MRI. The sequence was adjusted to maximize T1 contrast (TR = 40 ms, TE = 5 ms, flip angle 40°) and resulted in 128 contiguous slices 1–1.4 mm thick with an in-plane resolution of 0.9 × 0.9 mm within 20 min. In addition to multiplanar and surface postprocessing [12,17], segmentation of the brain from surrounding tissues and volumetric calculations were performed in five patients [16].

In group I, 14 patients underwent sequential localized ^{1}H spectroscopy. Also, sevén patients from groups II and III were examined using the STEAM sequence (TR = 1500 ms, TE = 136, 270 ms) as previously described [20]. Volumes of interest (VOI) for spectroscopy were selected directly from the T2-weighted images. Spectra were accumulated after optimization of the local magnetic field (shimming) without repositioning of the patient. The size of the sensitive VOI ranged from 16 to 27 ml and was always centered within the infarcted area. Spectra from normal volunteers from a preceeding study [13] served for comparison.

Overall examination time was typically less than 60 min and all patients agreed to undergo MR angiography, 3D-FFT FLASH, or MR spectroscopy after the technique had been explained to them.

MRI in Acute and Subacute Cerebral Ischemia

The MR appearance of cerebral ischemia is closely related to the underlying pathophysiology of the involved tissue. Arteriosclerotic cerebrovascular disease in general leads to a regional reduction of blood flow. Once the critical threshold of 20 ml/100 g per minute is reached, oxygen supply to the brain becomes insufficient and compensatory anaerobic glycolysis causes increasing tissue acidosis. Persistent ischemia leads to ATP depletion and the subsequent failure of the Na/K ATPase results in an electrolyte shift, paralleled by intracellular cytotoxic edema [6]. As the signal creation in MR depends on the amount and

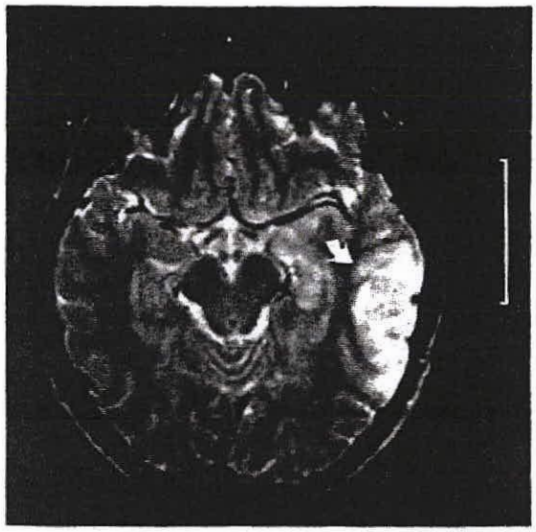

Fig. 1. T2-weighted image of a 63-year-old patient, 6 h after acute onset of aphasia Within the left temporal MCS territory there is T2 prolongation of the gyri most consistent with cytotoxic edma. In the anterior aspect signal abnormality has a tendency to spread into the white matter as an indicator of early vasogenic edema. *(arrow)*

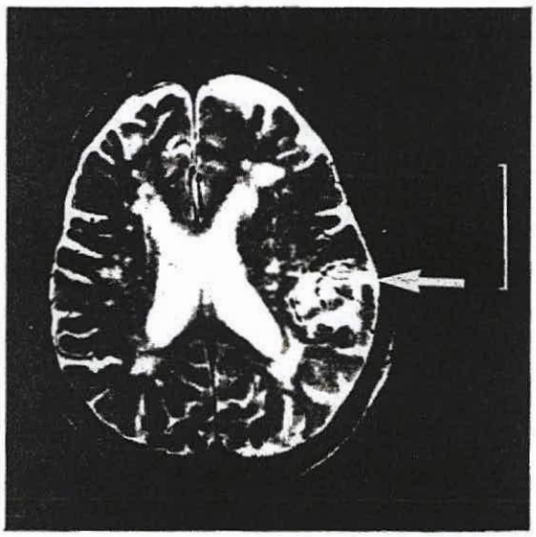

Fig. 2. 72-year old patient clinically presenting with moderate dementia and a history of transient right-sided weakness. T 2-weighted scan at the level of the lateral ventricles shows multiple small foci within the deep white matter, confluating adjacent to the frontal and occipital lobes. Neither signal behavior nor distribution is specific for cerebrovascular disease. However, the regional atrophy in the posterior MCA territory *(arrow)* points to the ischemic etiology of the lesions.

mobility of the ^{1}H atoms, MRI is most sensitive to this early stage of ischemic changes. According to the relative T1 and T2 prolongation, cytotoxic edema is best visualized on T2-weighted and proton density (PD) images. Cortical cytotoxic edema was present on the MR-scans in all patients who developed a permanent stroke in group I and were detected as early as 3 h after onset of symptoms (Fig. 1). Of the patients with transient neurologic deficit two exhibited signal alterations on T2-weighted images correlated to clinical symptoms.

Later on in the evolution of ischemia, extracellular water content of the tissue increases, leading to a combination of vasogenic and cytotoxic edema. Signal behavior of intra- and extracellular edema is similar, and differentiation is most often possible based on the finger-like spread of vasogenic edema along the white-matter tracts. In addition, vasogenic edema is accompanied by a more pronounced swelling of the brain, which may be further aggravated when tissue

is reperfused via collaterals or by recanalization of the previously occluded vessel. If restored blood flow meets vascular endothelium damaged by ischemia, petechial or even gross hemorrhage into the ischemic tissue is likely to occur. In the acute stage, presence of deoxyhemoglobin within the extravasated blood causes T_2 shortening of the protons which results in signal void on T2-weighted images. This effect is more pronounced at high field strength [21]. Gradient echo sequences, which are more sensitive to magnetic susceptibility effects, can compensate for this disadvantage of low-field magnets [9]. In the subacute phase methemoglobin is formed, yielding characteristic high signal intensity on either T_1- or T_2-weighted scans. Hemorrhagic transformation was seen in 19 of the group II patients on MRI, and the sensitivity was equal to that of CT.

Along with the disruption of the blood-brain barrier (BBB), the infarcted area is enhanced on T1-weighted images following Gd-DTPA administration. As Gd-DTPA has a comparable molecular weight to iodinated contrast agents, enhancement behavior on MRI resembles that known from CT.

MRI of Chronic Cerebrovascular Disease

Chronic regional infarction is characterized by postnecrotic cyst formation. Areas of incomplete infarction show neuronal loss, glial proliferation, and increased water content. Fluid-filled postnecrotic cysts behave similarly to cerebrospinal fluid (CSF) on MRI, appearing signal-intense on T2-weighted images and with low signal intensity on PD- and T1-weighted scans. Adjacent gliosis can be differentiated by relatively higher signals on the PD- and T1-weighted images.

Microangiopathy in chronic cerebrovascular disease (CVD) leads to minor perfusion of the watershed areas and development of small gliotic or cystic lesions. Predeliction sites are the basal ganglia and the deep white matter, where the vascular supply of the proximal middle cerebral artery (MCA) branches (end arteries) join the supply area of the perforating cortical anastomoses. Also common are ischemic lesions between the anterior cerebral artery (ACA) and the MCA, as well as the watershed area between posterior cerebral artery (PCA) and MCA. The lesions are often small and remain undetected on CT but the size varies widely and occasionally the lesions are confluent around the lateral ventricles. Signal behavior per se is unspecific (low or intermediate in T1-and high in PD/T2-weighted images) and differentiation from demyelinating disease may be impossible [29] (Fig. 2). To a minor extent, similar changes may be found in clinically normal elderly people [24]. However, a relationship to vascular risk factors has been described [26] and there is evidence that asymptomatic white-matter foci may represent a preclinical stage of CVD.

In five patients who underwent a 3D-FLASH examination the brain was isolated from the adjacent skull using a manually supported segmentation algorithm (Fig. 3). This new technique allows volumetric assessment of both infarction and remaining brain parenchyma with an accuracy in the range of less than a m^3 [16]. Calculation of the lesion size is not only important [7] in terms

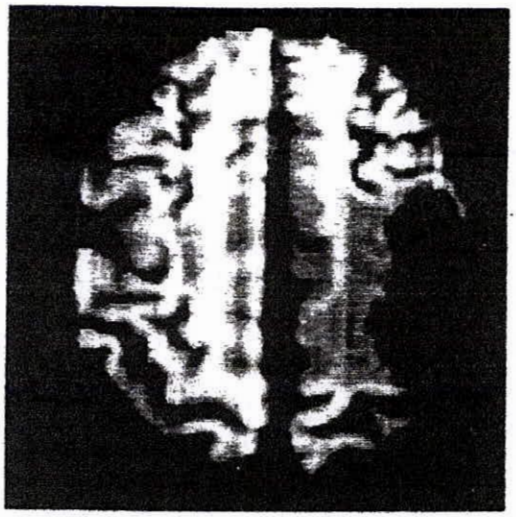

Fig. 3. Axial reformatted image from a 3D-FLASH acquisition after segmentation of the brain from surroundig tissues in a 59-year-old patient 2 years after infarction of the parietooccipital MCA territory. Volume of the remaining brain as well as the amount of tissue loss can accurately be calculated. T1 prolongation adjacent to the cystic infarct reflects gliosis

of prognostic information or neurologic correlation but offers a new rationale for monitoring the natural course and effects of pharmacotherapy in chronic CVD.

MR Angiography

The sensitivity of MR to moving spins has been known for a long time and is evident on every MR image [5]. MR angiography is a development which takes advantage of the inherent physical effects for clinical vascular diagnosis.

Initial studies using a 3D-FFT FISP sequence with gradient motion refocusing were performed on occlusive disease of the extracranial carotid arteries [11] and compared with noninvasive duplex Doppler ultrasound or X-ray angiography [27]. Stenosis and occlusion can be depicted in conjunction with routine brain MRI. Overestimation of the disease may result from turbulent flow, and postprocessing algorithms also harbor possible pitfalls [3]. Interpretation of MR angiography should therefore be done in clinical context and requires and broad knowledge of MR physics.

A more important application of MR angiography is directed toward the assessment of intracranial arteries, where ultrasound has obvious limitations [10,15]. Partial intracranial collateralization was demonstrated in most patients with extracranial carotid artery occlusion (Fig. 4). Seven patients suffering from acute infarction had evidence of intracranial vessel occlusion. Because of the spatial resolution provided by the sequence, 3D-MRA is applicable to the circle of Willis and proximal ACA, MCA, and PCA but not to small- vessel disease While anatomic resolution is favorable, time resolution of 3D-MRA is limited as well as the assessment of flow direction and selectivity to distinct vascular

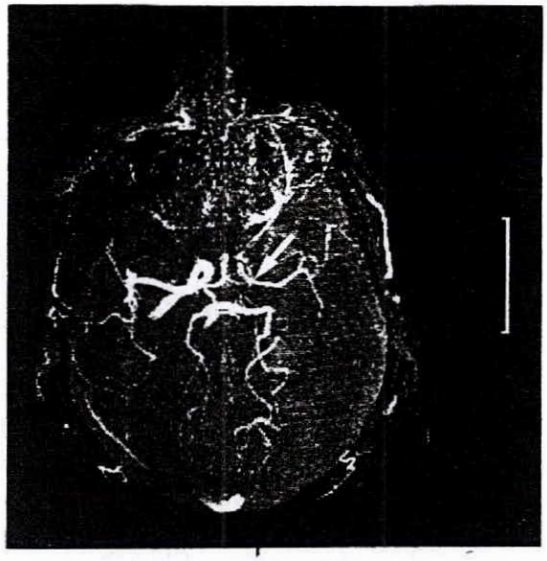

Fig. 4. MR angiography in a patient with subacute MCA infarction shows occlusion of the left internal carotid artery. The MCA on the *left* is collaterated via the circle of Willis (*arrow*)

territories [28]. In case of a pathologic MR angiogram, further evaluation by conventional angiography may be necessary.

Localized 1H MR Spectroscopy

At a field strength higher than 1.0 T, MR is not limited to the detection of water and fat protons but may also depict the protons bound to metabolites at less than millimolar concentration. The enormous concentration differences require suppression of the dominant water signal. Tissue volumes of 16–27 ml were directly selected from conventional MR images as the patient is not repositioned between imaging and spectroscopy.

At a TE of 270 ms, choline, phosphocreatine/creatine (PCr/Cr), and *N*-acetyl aspartate (NAA) but no lactate can be observed in a normal brain. Initial experiences of 1H MRS in acute stroke demonstrated abnormal increase of lactate within the ischemic area [4,9,13]. MR spectroscopy was performed in a selected group of 14 patients with territorial MCA infarction [18] (Fig. 5). Lactate, indicating anaerobic glycolysis, was the dominant resonance during acute ischemia (3–8 h after onset of symptoms and up to 3 weeks). On the first day, PCr/Cr remained at normal levels, presumably because glycolysis fuels ATP production. Later on PCr/Cr decreases and is paralleled by further lactate increase and NAA depletion. NAA seems to represent a potential marker for neuronal viability [8] (Fig. 6). The spectra from patients who were investigated in the chronic stage of cystic infarction showed no metabolites. Chronic gliotic areas did not show lactate but an overall reduction of metabolites when compared with normal brain.

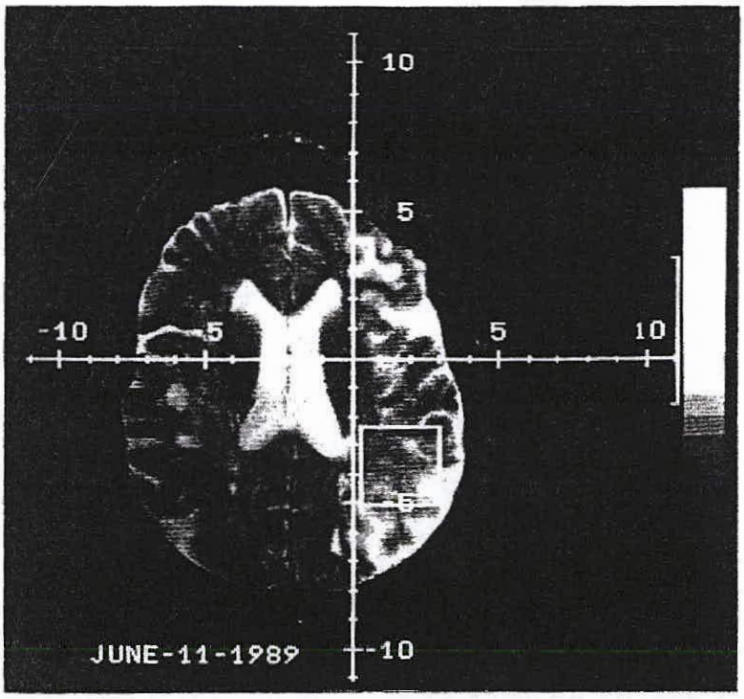

Fig. 5. 62-year-old female suffering from acute hemiplegia of the right side and global aphasia. T2-weighted MRI 4 h after onset of symptoms reveals T2 prolongation, indicating cytotoxic edema in the whole cortical MCA distribution. There is also evidence of chronic ischemic changes in the contralateral hemisphere. The *box* indicates the location of a 27-ml VOI selected for localized ^{1}H spectroscopy

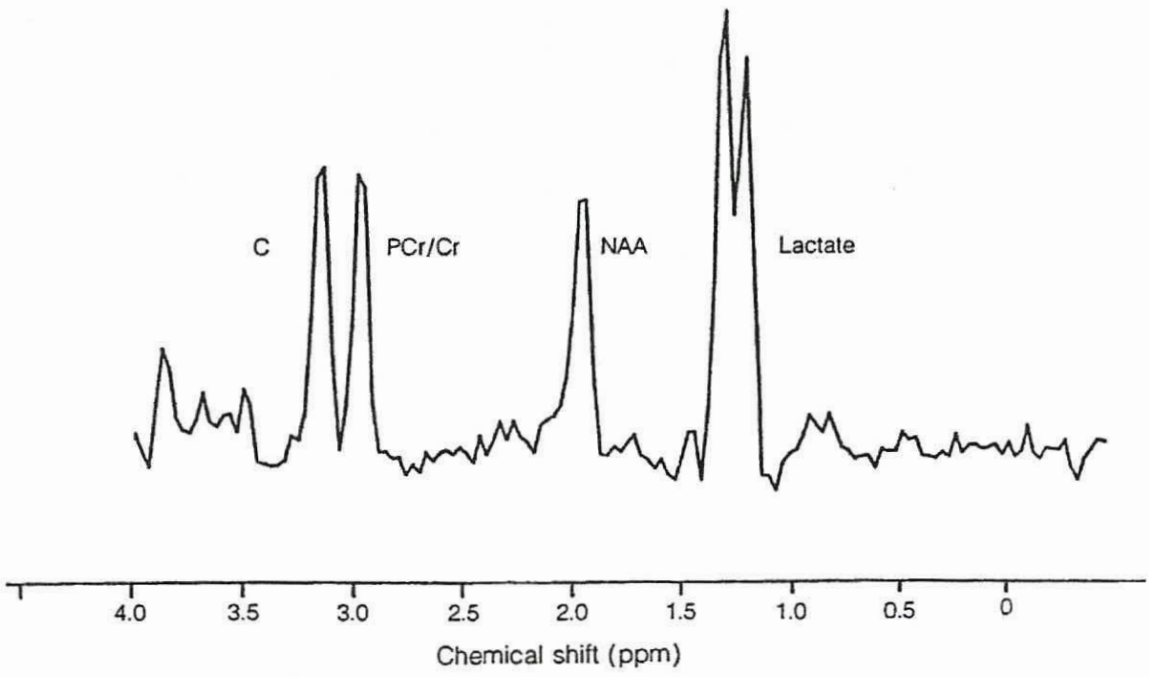

Fig. 6. Localized ^{1}H spectrum (TR = 1500 ms, TE = 270 ms) exhibits a significant increase of *lactate*, indicating anaerobic glycolysis. In parallel there is decrease in -acetyl aspartate (*NAA*). The remaining resonance of NAA and the level of the phosphocreatine/creatine (*pCr/Cr*) peak demonstrate the partially preserved structural metabolism in the presence of positive imaging findings and complete clinical deficit.

Discussion

MRI proved to be more sensitive than CT in the detection of focal postischemic changes, both in terms of lesion size and in terms of anatomic distribution, especially with respect to the posterior fossa. The major advantage, however, is the possibility of visualizing ischemia as early as 3–4 h after onset of clinical symptoms. Although the signal appearance might not be specific for postischemic changes, the improved assessment of regional distribution, together with the neurologic presentation and history, enables a conclusive diagnosis in most cases.

Adequate assessment of tissue loss and overall or regional brain volume is possible using high-resolution 3D-FLASH sequences. MR angiography is now a routine procedure and allows the noninvasive estimation of major vessel pathology. X-ray angiography will not be completely replaced, but indications for its use will change in future. Presumably, MR angiography will serve as a vascular screening method and may provide a new rationale for the indication of regional fibrinolysis. With the advent of localized 1H MR spectroscopy, ischemic metabolism can be observed without the necessity of administering radioisotopes. Conclusions can be drawn about the presence of anaerobic glycolysis and NAA may serve as a marker for the viability of neurons within the ischemic area. For the first time, noninvasive monitoring of the effects of pharmacotherapy may become a reality.

In summary, MR is definitely an unique approach to CVD, providing access to morphology, macrocirculation, and metabolism for therapeutic management in a single examination. There is no further need to move the patient from one diagnostic procedure to the other. Time can thereby be saved, which is mandatory for the early institution of therapy.

At present, there is no definitive treatment for acute stroke, but MRI, MR angiography, and MR spectroscopy will help to subcategorize patients for therapeutic decisions and more sophisticated pharmacotherapeutic studies in future.

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