MR Imaging for Acute Stroke

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Abstract Cerebral imaging is essential to differentiate the pathologies behind acute stroke. Excluding hemorrhage with a native CT is a prerequisite before thrombolytic drugs can be administered. With stroke MRI, vessel occlusion, ischemia and infarction can be visualized. This detailed diagnostic information can facilitate the decision for or against thrombolysis. Analysis of FLAIR and diffusion-weighted images enables the identification of patients in an early time window after ictus and is currently used in randomized trials of wake-up stroke.

Keywords Stroke · Cerebral imaging · MRI · Thrombolysis · FLAIR · Diffusion weighted images · Wake-up stroke

Introduction

Focal or general neurological symptoms of a vascular origin termed “stroke” can be based on cerebral ischemia and on intracerebral or subarachnoid hemorrhage (SAH). Thunderclap headache and generalized symptoms point to SAH. Hemiparesis, visual or speech disturbance are typical symptoms of both ischemia and parenchymal hemorrhage. Thus, imaging-based exclusion of hemorrhage is the

minimal requirement before the only etiological treatment can be initiated. Thrombolysis is a highly efficient treatment in ischemic stroke, saving patients from permanent disabilities. In pooled data from 2,775 patients treated in placebo-controlled rt-PA trials, more patients had an independent clinical outcome when rt-PA was administered. The earlier rt-PA was provided, the higher the likelihood of treatment response [1]. Providing the treatment solely based on clinical examination and exclusion of hemorrhage has an OR of 2.55 for response when rt-PA is administered within 90 min of ictus. The clinical benefit of rt-PA versus placebo decreases over time (91–180 min = OR 1.64/181–270 min = OR 1.34). In addition, there is an increase of drug-related parenchymal hemorrhages (PH2), worsening long-term clinical outcome. The risk of PH2 ascends with delay from an OR 3.6 (181–270 min) to 4.32 (271–360 min).

The decline of efficiency and increase of side effects corroborate the stroke theorem “time is brain.” Consequences for neuroimaging in acute stroke are:

- (1) Excellent imaging work flow is essential to facilitate good treatment response;
- (2) Stroke imaging research must not delay drug administration;
- (3) Complex imaging protocols are justified only in cases with clinical uncertainties.

MRI has the potential to fulfill these requirements. However, allowing acute stroke patients to derange a busy MRI schedule is a strategic decision and providing stroke MRI during afterhours requires appropriate resources. A standard stroke MRI protocol has an acquisition time of less than 10 min [Scout 10 s/T2* 2 min/diffusion weighted MR-imaging (DWI) 30 s/FLAIR 2 min/perfusion imaging 1 min]. Starting the protocol with a T2*-weighted sequence

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followed by DWI provides the minimal required imaging information within 3 min. At our institution, we administer the rt-PA bolus in the MRI scanner once hemorrhage and very large infarction have been excluded. Additional sequences and research protocols can be conducted once treatment has been initiated. If patients are diagnosed with unexpected pathologies such brain tumor, venous thrombosis, abscess or encephalitis, they receive adapted examinations.

DWI in Ischemic Stroke

Diffusion-weighted MR-imaging (DWI) represents the Brownian motion of water molecules in tissues. The random motion of water molecules in living tissues gives low signal. Adding two diffusion gradients to a T2-weighted sequence causes a loss of signal from moving protons; static protons are refocused, leading to high signal intensity. Moseley et al. [2] demonstrated hyperintense signal on DWI in a cat model of ischemic stroke. The reduced Brownian motion in ischemic tissue is caused by a shift from extracellular matrix into cells after membrane ion pump failure. Applying diffusion sequences with different gradient intensities (*b*-value) allows quantification of diffusion. Ischemic stroke has been diagnosed in humans with DWI since 1995 using complex motion correction techniques [3]. Introduction of fast gradient technology echo planar imaging reduced scan time for whole brain DWI down to 30 s.

Cytotoxic edema occurs within minutes of severe metabolite shortage, thus allowing very early detection of infarction using DWI. On a native CT, a net water uptake of brain infarction leads to a loss of tissue density of 0.4 HU/h [4], enabling a median sensitivity of 64 % within 6 h

of stroke [5]. On DWI, the signal intensity is based on a shift from extra- to intracellular. Thus, more molecules are restricted by the cytoskeleton and organelles, and there is less extracellular space for free Brownian motion. No net water uptake is required to observe hyperintensities on DWI, and the simple shift of water leads to decreased diffusion. However, diffusion in the extracellular matrix is intense along fiber tracts and restricted in the perpendicular direction. To compensate anisotropic diffusion in tracts, DWI measurement is conducted in at least three orthogonal directions. The mean value of these measurements leads to isotropic DWI.

DWI is typically conducted with a short scan time, and this robust technology provides good lesion-to-normal tissue contrast in territorial infarction. In patients presenting without disabling deficits or only with transient ischemic attacks, and in case of suspected brain stem infarctions, the standard slice thickness of 5 mm is inappropriate. High-resolution DWI with 2.5–3-mm slice thickness and a *b*-value ratio (0 and 1,000 s/mm²) of 1:5 or 1:6 provide significantly increased signal-to-noise and contrast-to-noise ratios [6]. In a cohort of 42 patients, the incidence of patients with more than five small lesions was increased from 19 to 42 %. Extending scan time beyond 4 min enables detection of more lesions. If they were located in multiple territories, this is a diagnostic hint indicating emboli (Fig. 1).

A significant number of DWI-negative strokes have been reported using standard DWI (slice thickness 5 mm with 2 mm gap), of which ≤ 23.1 % show DWI lesions on follow-up [7]. To overcome this diagnostic failure, Hotter et al. performed follow-up examinations in a cohort of 63 patients presenting with acute cerebrovascular events but

Fig. 1 hr DWI shows a very small infarction in the medulla oblongata (a). Punctate infarctions affecting different territories (b, c) indicate a proximal source of emboli

negative acute DWI within 24 h of ictus. Persistence of symptoms the other day had an OR of 17.5 for new infarction. Using NIHSS to triage for follow-up MRI would have led to a false-negative rate of 3.2 %, with an overall reduction of examinations of 81.0 %. This is further expressed by a negative predictive value of 96 % [8•].

Stroke MRI to Identify Hemorrhage

The main differential diagnosis for brain ischemia is intracerebral hemorrhage (ICH). Based only on clinical examination, these two pathologies cannot be distinguished. Thus imaging is essential before any treatment decision can be made in acute stroke. Two multicenter studies investigated the diagnostic accuracy of stroke MRI in cerebral hemorrhage. Kidwell et al. [9] conducted an observational cohort study in 200 consecutive stroke patients. Both on CT and MRI, 31 patients were diagnosed with acute ICH; however, in three of these patients, this differed from the discharge diagnosis. The authors concluded that both modalities are as accurate in patients presenting with acute stroke for the detection of acute hemorrhage. In a multicenter study on ICH, Fiebach et al. [10] evaluated the diagnostic accuracy of acute MRI when interpreted by experts and final year medical students. Based on standardized stroke MRI protocols from 6 university hospitals, imaging studies from 62 ICH patients and 62 nonhemorrhagic stroke patients, all imaged within the first 6 h after symptom onset were analyzed. The experts identified ICH with 100 % sensitivity and accuracy.

Students reached a mean ICH detection sensitivity of 95.16 % (CI 90.32–98.39). For post-interventional monitoring of hemorrhagic transformation and parenchymal hemorrhage, the same MR sequences can be employed, and classification of hemorrhagic changes according to ECASS CT criteria have been published [11•] (Fig. 2).

With new susceptibility-sensitive MR sequences, readers should be aware of other entities causing a signal loss on T2*-weighted images. “Small foci of chronic blood products in normal (or near normal) brain tissue” [12] with diameters up to 10 mm are interpreted as chronic microbleeds. These iron-rich deposits can be seen in >10 % of elderly healthy individuals. Prevalence depends on sequence technique and slice thickness. Fiehler et al. [13••] investigated whether chronic microbleeds are associated with an increased risk of secondary symptomatic intracranial hemorrhage (SICH) after thrombolytic therapy. They analyzed MRI data from 570 thrombolized patients. Chronic microbleeds had a prevalence of 15.1, and 5.8 % of CMB-positive patients had SICH compared to 2.7 % in patients without chronic microbleeds. This non-significant difference is unlikely to exceed the benefits of thrombolytic therapy; thus, chronic microbleeds should not be misinterpreted as a contraindication to fibrinolytic treatment.

Mismatch and Its Limitations

In MRI imaging of acute stroke patients, the mismatch concept is based on the assumption that a hyperintensity on DWI shows the area of irreversibly injured tissue, whereas

Fig. 2 Acute MRI shows DWI lesions at the insular and caudate nucleus (a) and severe MTT prolongation in the MCA territory (b); 20 h after thrombolysis hemorrhagic transformation can be seen in the initially infarcted tissue on T2* weighted images (c). At 3 T hemorrhagic transformation causes a homogeneous signal loss. In contrast to parenchymal bleeding, there is no surrounding edema visible

perfusion imaging shows an area of reduced cerebral perfusion [14], with the mismatch between the two areas representing the ischemic penumbra [15]. As iv rtPA has become the standard treatment in the acute 4.5 h time window for patients independent of individual characteristics, the mismatch concept sought to establish its worth in selecting candidates for tPA beyond this rigid time window, guided by the idea of individually tailored treatment. Data extracted from large patient samples hinted at this being a safe, sane and worthwhile approach [16]. Therefore, the mismatch hypothesis commenced its journey as a prominent topic of investigation if not inclusion criterion in a number of studies dealing with acute ischemic stroke and has even found its way into clinical practice [17, 18]. To name a few examples, the DEFUSE study (published in 2006) introduced the “target mismatch” concept: a subgroup of patients with a profile of a DWI lesion smaller than 100 ml with at least 10 ml and 20 % of mismatch, who were especially likely to benefit from reperfusion therapies (DEFUSE), whereas the DIAS trial (published in 2005) used the 20 % mismatch as an inclusion criterion and showed an association with higher reperfusion rates and better clinical outcome in mismatch patients treated with desmoteplase as compared to placebo (DIAS). However, the several multicentric studies which had been conceptualized around the mismatch hypothesis and its benefit for selecting patients for thrombolysis (DEFUSE, DIAS, DIAS II) also pointed to the many pitfalls of perfusion imaging, the first one being the very definition of mismatch. The initially popular idea that a sufficient mismatch was a difference of 20 % or more between PI and DWI soon proved too lenient [19] and likely played a pivotal role in ensuring the negative outcome of the DIAS II trial (published in 2009). Additionally, unlike DWI, perfusion imaging is not straightforward as the depiction (and subsequent potential volumetric assessment) of hypoperfusion is based on an array of different parameter maps and underlying calculation methods. Despite many studies that have dealt with the issue of comparing these, there is still no scientific consensus on which parameter, method of delineation or calculation technique should ideally be used [20]. Despite these obstacles, the mismatch hypothesis remained popular, owing no doubt to its elegance and common sense, resulting in further trials being undertaken to prove its value for patient selection. The DEFUSE II trial (DEFUSE II) modified the mismatch-based inclusion criteria inherited from its predecessor, the DEFUSE trial, by taking the before-mentioned pitfalls into account. They have used a stricter hypoperfusion definition as well as a stricter definition of mismatch, allowing only patients showing a minimum of 80 % and 15 ml mismatch as well as less than 100 ml of severely hypoperfused tissue to be selected in the “target mismatch” group.

Subsequently, they have shown that more than half of all patients who belonged to the “target mismatch” profile and also achieved reperfusion ended up with a favorable clinical outcome. However, the rather small number of patients with no target mismatches in their study greatly limited any ability to characterize the response to reperfusion in non-mismatch individuals. As a conclusion, the mismatch concept appears to function and provide useful information, but only under certain conditions, one of them being a large enough absolute mismatch volume, of somewhere between 15 and 60 ml, providing a sufficient amount of tissue to be saved in order for the results of successful reperfusion to be demonstrated [19]. Another would be a strict enough definition of hypoperfusion, serving to prevent areas of benign oligemia from being misinterpreted as tissue at risk of infarction [21, 22]. As a third criterion, one should be watchful of the absolute volume and severity of hypoperfusion, as there appears to be an invisible line beyond which tissue is so compromised that the condition stands to deteriorate rather than improve after thrombolytic therapy (DEFUSE, EPITHET).

MR Angiography (MRA) in Ischemic Stroke

Obstruction of a major intracerebral artery is the typical reason for territorial infarction. Although small vessel occlusion can cause severe symptoms if affected fibers are essential, the main therapeutic target of thrombolytics is acute large vessel disease. De Silva et al. [23] pooled the results of two MRI-based trials to investigate the impact of large vessel obstruction on the infarct development. Forty-eight patients who were treated and 24 patients receiving placebo had arterial obstruction on MRA. An additional 33 patients receiving rt-PA without any obstruction on MRA and 11 receiving placebo presented without occlusion. For the obstruction subgroup, 26 ml less lesion growth was observed after rt-PA treatment, while no difference was seen for patients without an MRA target.

In a single-center prospective study, Ma et al. [24] offered rt-PA to patients who presented 3–6 h after symptom onset if vessel occlusion and perfusion–diffusion mismatch were present and the DWI lesion was smaller than 100 ml. Out of 54 patients presenting with such a “salvageable pattern” on MRI, 32 chose rt-PA, while 22 refused thrombolytics. An additional 35 patients with a no-occlusion pattern presented with less baseline stroke severity. Seventy-five percent of no occlusion patients experienced favorable outcomes. In salvageable pattern patients, a favorable outcome was reached by 50 % of rt-PA patients in contrast to 22.7 % in the subgroup who refused treatment.

Additional hints toward vessel status-based treatment with thrombolytics were seen in a post hoc evaluation of

data from the DIAS 2 trial, which employed a 20 % PI-DWI mismatch for patient selection. Fiebach et al. [25•] grouped DIAS/DEDAS/DIAS2 patients according to their initial vessel status. Forty percent of patients with vessel occlusion or severe stenosis treated with a 6 h 40 min median delay from symptom onset reached an independent clinical status at day 90 in contrast to a 16 % responder rate in the placebo group. This 24 % difference in clinical response to desmoteplase versus placebo led to an odds ratio of 4.1 for favorable outcome. Studies to investigate the desmoteplase response with recruitment primarily based on initial vessel status are ongoing.

Fluid-Attenuated Inversion Recovery (FLAIR) in Wake-Up Stroke

International guidelines and approval criteria for use of intravenous thrombolysis exclude patients with stroke whose time of symptom onset is unknown [26]. The use of a time window for tPA eligibility arises from evidence gathered through thousands of patients showing the declining benefit of thrombolytic therapy with time, with the cutoff lying at around 4.5 h after stroke onset, beyond which time it appears that treatment no longer leads to an increased odds ratio for favorable outcome [27•]. However, not all patients are aware of, or able to articulate, the exact time when their symptoms began. It is presently estimated that as many as 25 % of all ischemic strokes occur during sleep [28, 29]. Based on current guidelines for stroke management, these patients are excluded from thrombolytic treatment, although they may well be, without knowing it, within the approved time window. Luckily, modern MR imaging appears capable of estimating

the time from stroke onset, and researchers have already stepped forward offering a solution. As far back as the mid-1990s, it has been proposed that an assessment of signal changes on FLAIR images in the areas showing a diffusion restriction on DWI may provide an estimate of ischemic lesion age [30]. The resulting concept was that, in patients with acute ischemic stroke, the combination of a lesion's visibility in DWI and parallel invisibility in FLAIR (the so-called DWI-FLAIR mismatch) could predict symptom onset under 4.5 h (Fig. 3). This theory has since been put to the test in a number of small, independent studies [31–33], which showed sufficient promise to warrant serious multicenter investigation. PRE-FLAIR (published in 2011) was precisely such a study, retrospectively assessing the DWI-FLAIR mismatch hypothesis in several hundred patients from centers across the globe [34]. They have shown, with high specificity and positive predictive value, that patients with a DWI-FLAIR mismatch were likely to be within a time window for which thrombolysis is safe and effective. Naturally, like most medical concepts, the DWI-FLAIR mismatch has its drawbacks. Although there is a general consensus that lesion conspicuity on FLAIR increases with time [35], this temporal dependence does not appear to follow any mathematical model. Accordingly, relative signal intensity measurements of FLAIR lesions show only a moderate correlation with time from symptom onset [36••], for which reason the idea of automating the mismatch decision by selecting a threshold value for a lesion's "FLAIR visibility" had to be abandoned in favor of a continuing visual assessment done by attending physicians. Visual evaluation, in turn, suffers from subjectivity leading to suboptimal interpreter agreement, mostly owing to subtle hyperintensities being less reliably

Fig. 3 DWI FLAIR mismatch in a WAKE-UP patient. The acute infarction causes decrease of Brownian motion in the anterior insula and the frontal operculum on DWI. On FLAIR the same tissue has no signal alteration. Note the hyperintense vessel signs on FLAIR indicating slow collateral flow

categorized [35, 37]. Additionally, it was recognized that larger DWI lesion volumes serve as independent predictors of lesion visibility on FLAIR imaging, tipping the scale toward a verdict of DWI–FLAIR match [34]. Last but not least, although supratentorial stroke has been the main focus of research, there have been hints that infratentorial lesions exhibit a different behavior with regards to the gradual increase in FLAIR signal intensity and may therefore not be suitable for assessment using the DWI–FLAIR mismatch in the same way that their supratentorial counterparts are [37].

Despite these issues, a prospective investigation of the usefulness of the DWI–FLAIR mismatch in the treatment of patients with unknown time of symptom onset was warranted. The ongoing WAKE-UP trial [38] has just entered its second year of patient enrollment, and its final results are eagerly awaited.

Conclusion

In conclusion, MRI offers an exquisite amount of structural and physiologic information in acute stroke patients that is essential to the diagnosis of these patients and that might be used to guide acute reperfusion therapy. A number of ongoing clinical trials have been designed to validate such an approach to MRI-guided stroke therapy.

Compliance with Ethics Guidelines

Conflict of Interest JB Fiebach serves on the imaging board for Lundbeck, is a consultant for Lundbeck, BioClinica, and Synarc and has received a speaker honorarium from Siemens and Boehringer Ingelheim. I Galinovic was an investigator for the WAKE-UP study.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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