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Case Report

Case Report of a Diffusion-Weighted Magnetic Resonance Imaging Negative Patient with an Acute Occlusion of a Large Intracranial Artery

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Abstract

Diffusion weighted imaging (DWI) sequences in ischemic stroke (IS) are sensitive and helpful to detect even small vascular lesions. As a restriction, the majority but not all IS patients show a DWI lesion at the time of imaging in the acute stroke setting. We present one of the rare cases of a DWI negative patient with an acute occlusion of a large intracranial artery. We discuss the strengths and limitations of DWI magnetic resonance imaging (MRI) in IS and conclude that negative DWI in patients with a typical clinical presentation for stroke should be a reason to consider a stroke mimic but must not principally restrain the treating physician from thrombolysis.

Keywords: Ischemic stroke; Middle cerebral artery occlusion; Magnetic resonance imaging; Diffusion-weighted imaging; Wake-up stroke

Abbreviations

DWI: Diffusion-Weighted Imaging; IS: Ischemic Stroke; MRI: Magnetic Resonance Imaging; rt-PA: Recombinant Tissue Plasminogen Activator; NIHSS: National Institutes of Health Stroke Scale; TOF: Time-of-Flight; MCA: Middle Cerebral Artery; ACA: Anterior Cerebral Artery; DSA: Digital Subtraction Angiography; MT: Mechanical Thrombectomy; FLAIR: Fluid Attenuation Inversion Recovery

Introduction

Two decades ago large clinical trials led to the approval of recombinant tissue plasminogen activator (rt-PA). While in these trials CT imaging has been mainly or even exclusively used to assess for inclusion and exclusion criteria [1], today MRI including DWI is increasingly available in acute stroke settings. Therefore, on one hand, additional diagnostic information will be generated; on the other hand, novel challenges regarding identification of eligible patients for thrombolysis may arise. This case is intended to sensitize the readers for the underlying pathophysiology as well as the chances and pitfalls of diffusion-weighted MRI in acute IS.

Case Presentation

An 88-year-old woman with past medical history significant for arterial hypertension, hyperlipidemia, and chronic heart failure and ischemic stroke has been found in the morning lying in her bathroom unable to walk. In the emergency room the patient was drowsy, showed a right-sided hemiparesis with central facial palsy and non-fluent aphasia adding up to 15 points on the National Institutes of Health Stroke Scale (NIHSS). The initial computed tomography scan of the brain did not demonstrate hemorrhage or hypodensities suggestive for early signs of IS. Immediately, MRI including DWI and fluid-attenuated inversion recovery (FLAIR) sequences, as well as a time-of-flight (TOF) intracranial angiography was performed. Last seen normal and symptom onset remained unclear but between emergency call and first MRI sequence at least 82 minutes elapsed. While there were no signs of acute IS in DWI (not shown) and only moderate white matter lesions in FLAIR images (Figure 1A), TOF angiography revealed an occlusion of the left proximal middle cerebral artery (MCA, Figure 1B). Due to the proximal MCA occlusion and the severe clinical condition we decided to treat the patient with intravenous rt-PA despite unknown symptom onset. In parallel, conventional digital subtraction angiography (DSA) was done according to the bridging-concept and confirmed the MCA-occlusion (Figure 1C). Mechanical thrombectomy using an Acandis Aperio® stent-retriever (4.5x40 mm) was successfully performed under general anesthesia (Figure 1D,E). During the intervention, a clot fragment entered the left anterior cerebral artery (ACA) but was retrieved immediately. A follow-up MRI scan two days later showed a DWI lesion suggestive for an acute IS in the left corpus callosum representing ACA territory (Figure 1F). Despite the proximal MCA occlusion there was no DWI lesion in the left MCA territory. Diagnostic work-up revealed atrial fibrillation as most likely stroke etiology. The patient recovered well and was discharged home to independent living after 6 days without any neurological deficit (NIHSS 0).

Discussion

Development and magnetic resonance imaging of cytotoxic edema in ischemic stroke

In vivo animal [2] and human [3] studies showed that DWI lesions represent the inflow of water into the intracellular compartment upon disruption of mitochondrial oxidative phosphorylation, loss of high energy phosphates and increase in inorganic phosphate and lactate. These pathophysiological mechanisms lead to neuronal transmembrane Na+/K+ transport failure, resulting in a shift of fluid and sodium from the extracellular to the intracellular compartment [2]. Importantly, neurological symptoms may occur before ion pump failure and cell swelling starts [4]. Therefore, from a pathophysiological

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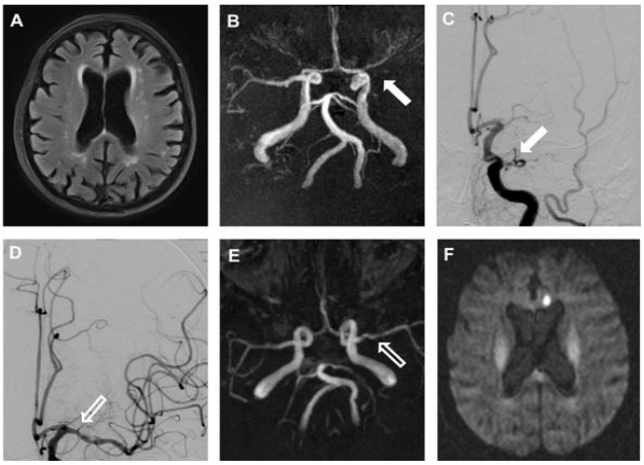

Figure 1: Magnetic resonance imaging (MRI, 3.0 T, Trio, Siemens, Germany) of the brain (different sequences) and DSA of the brain-perfusing vessels before and after mechanical thrombectomy (MT).
A) FLAIR sequence immediately after patient admission showing age-appropriate white matter lesions. The initial DWI sequence was negative (not shown).
B) TOF angiography showing a proximal occlusion of the left middle MCA (solid arrow).
C) DSA confirming the MCA occlusion on the left side (solid arrow).
D) DSA after MT proving patent left MCA (open arrow), grade 2B according to the thrombolysis in cerebral infarction (TICI) grading system.
E) TOF angiography confirming patent left MCA (open arrow).
F) diffusion-weighted MRI sequence two days after patient admission showing an infarction in the ACA territory, caused by clot migration during MT (white spot).

perspective, neurological deficits in context of acute IS may be present without a DWI lesion. In addition, collateral status and consequently cerebral blood flow despite arterial occlusion can be assumed to play a major role for the development of DWI lesions.

After approximately 4-5 hours a FLAIR lesion develops representing the subacute vasogenic edema after IS [5].

Strengths of diffusion-weighted magnetic resonance imaging in ischemic stroke

Higher spatial resolution especially in the brainstem and posterior fossa contributes to the higher sensitivity of MRI for detection of IS lesions compared to CT. Moreover, DWI is considered to show IS lesions within minutes after symptom onset with increasing probability of positive DWI findings over time [6]. It is important to note that the majority of IS patients present with an early positive DWI signal in initial MRI [4]. *Vice versa*, it has been suggested to consider patients presenting with acute neurological deficit and negative DWI findings as possible stroke mimics prior to assuming a MRI negative stroke [7].

Furthermore, DWI imaging is a prerequisite for sophisticated MRI protocols analyzing various mismatch strategies in selected patients with IS aiming to prolong the time-window of intravenous thrombolysis (DWI-Perfusion-mismatch, DIAS trials) [8] or to investigate intravenous rt-PA treatment in wake-up situations with unknown symptom onset (DWI-FLAIR-mismatch, e.g. WAKE-UP trial: NCT01525290) [7]. For the latter mismatch concept a DWI lesion without a correlation in FLAIR sequences is required as inclusion criterion.

Limitations of diffusion-weighted magnetic resonance imaging in ischemic stroke

There are also a number of limitations of DWI imaging in IS that vascular neurologists have to keep in mind to prevent overreliance on that imaging technique. A review comparing the relation between acute DWI imaging and final infarct volume showed that consideration of a DWI lesion as the irreversibly lost ischemic core is troublesome as acute DWI lesions either over- or underestimated the final infarct volume [9].

Furthermore, several authors reported IS without DWI abnormalities ranging from 2.2% to 29% for either posterior circulation, lacunar [10] or non-disabling IS [4]. For the anterior circulation there are only few reports mainly of patients with minor IS and initial negative non lacunar DWI sequences [6]. Even less publications are available on disabling IS [11,12] and only a few cases are reported of DWI negative patients with an acute occlusion of a large intracranial artery [13].

Importantly, in a one year follow up in minor IS patients no difference regarding clinical outcome could be observed between acute IS patients with *vs.* without DWI lesions, arguing strongly against prognostic estimation based on DWI status and the hypothesis (sometimes even clinical practice) to exclude IS based on negative DWI [4].

Conclusion

DWI sequences in IS are sensitive and helpful to detect even small vascular lesions. Nevertheless, exclusion of IS in patients with negative DWI but symptoms typical for stroke is not possible. Therefore, negative DWI is no reason to principally withhold thrombolysis. As seen in our case, a TOF angiography might give important clues for the diagnosis of IS and should therefore be conducted also in patients with negative DWI.

It is an open question if rt-PA treatment is safe and effective in patients without DWI lesion beyond the 4.5h time-window. Randomized-controlled trials in DWI negative stroke patients who exceeded the 4.5h time-window would be needed. Based on

pathophysiological considerations, intravenous rt-PA treatment in a patient without DWI (and without corresponding FLAIR) lesion can be assumed to be safe as a major impairment of the blood-brain barrier can be excluded [14].

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