Case Report

Tissue Plasminogen Activator for Cortical Embolism Stroke with Magnetic Resonance Perfusion Imaging: A Report of Two Cases

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Keywords

Acute ischemic stroke · Diffusion-weighted imaging-negative acute ischemic stroke · Recombinant tissue plasminogen activator · Magnetic resonance perfusion · Diffusion-weighted image-perfusion-weighted image mismatch

Abstract

Computerized tomography (CT) or magnetic resonance imaging (MRI) is indispensable for diagnosing acute ischemic stroke (AIS) patients who are candidates for recombinant tissue plasminogen activator (rt-PA) therapies, but further investigation concerning appropriate selection of therapy following advanced imaging including perfusion imaging has not yet been done. The 2018 AHA guidelines have recommended not to perform excessive time-consuming imaging before rt-PA. Here we describe two cases in which reperfusion therapy was decided based on advanced imaging. The first case was a 70-year-old woman with complaints of total aphasia and right unilateral spatial neglect. Her MRI revealed no apparent high signal area in diffusion-weighted image (DWI), and her magnetic resonance angiography (MRA) showed no large vessel occlusion. Subsequent perfusion-weighted image (PWI) analysis showed a unilateral perfusion deficit in the left middle cerebral artery (MCA) region. The other case was an 88-year-old man with complaints of minor unilateral spatial neglect, right conjugate deviation of the eyes, and dysarthria. His MRI also revealed no apparent high signal area in DWI, and MRA showed slight stenosis in the right middle MCA. Subsequent PWI analysis showed a unilateral

perfusion deficit in the right MCA region. In both cases, intravenous rt-PA therapy was administered after the diagnosis of AIS and the patients responded well to the reperfusion therapy. When DWI is performed too early, detecting the ischemic core and differentiating between a diagnosis of stroke and stroke mimics is sometimes difficult. Evaluation of perfusion abnormalities in acute cases can be performed quickly, as shown in these cases. Although rt-PA can be given just by non-contrast CT with no hemorrhage, advanced imaging may be an option to identify difficult-to-diagnose patients who require reperfusion therapy.

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Introduction

Computerized tomography (CT) or magnetic resonance imaging (MRI) is indispensable for recombinant tissue plasminogen activator (rt-PA) therapies, but the usefulness of multimodal imaging including perfusion imaging has not been thoroughly investigated in all terms. The 2018 AHA/ASA Guidelines for the Early Management of Patients with Acute Ischemic Stroke has referred to the use of multimodal imaging including perfusion imaging as HARM for the possibility of delaying administration of intravenous rt-PA in the 4.5-h time window. The time required for imaging workflow may sometimes be deleterious to patients with acute ischemic stroke (AIS) [1]. On the other hand, multimodal imaging including perfusion imaging analysis has not yet been standardized in Japan and very few institutions perform perfusion imaging for stroke imaging analysis in variable time windows. The rate of intravenous rt-PA is around 5–7% in Japan [2], which is less than other countries, and all options are needed to maximize these numbers. One reason for this low number in Japan is that approximately 10% of acute stroke care hospitals in the Japanese medical service region cannot perform intravenous rt-PA, and lack of stroke neurologist is a serious issue. Here, we present two cases that highlight the usefulness of perfusion mismatch analysis software as an option to define the diagnosis of AIS. These cases had certain neurological deficits but atypical, and negative diffusion-weighted imaging (DWI) results may have misdiagnosed these cases as stroke mimics. In these cases, perfusion imaging led to a definite diagnosis of AIS.

Case Presentation

Case 1

A 70-year-old woman presented to the emergency room with symptoms of total aphasia and right unilateral spatial neglect. She had a history of bronchial asthma, dyslipidemia, and type 2 diabetes. Dyslipidemia and type 2 diabetes were noted from the age of 62. The onset of symptoms was 46 min prior to presentation to the emergency room. Her neurological findings confirmed mixed aphasia (she could not obey simple commands), neglect of the right half of her body, and left conjugated deviation. No obvious paralysis or sensory disturbances were noted. Deep tendon reflex was normal, and no pathological reflex was observed. Her NIH Stroke Scale (NIHSS) was 7. Her baseline MRI revealed no obvious high signal in DWI (Fig. 1a). Fluid-attenuated inversion recovery (FLAIR) confirmed FLAIR vessel hyperintensities in the left middle cerebral artery (MCA) (Fig. 1b). Magnetic resonance angiography (MRA) showed partial obstruction in the distal part of the left MCA (Fig. 1c), which may have been an artifact. To make a definitive diagnosis, perfusion-weighted imaging (PWI) was additionally performed to assess the tissue at risk. Our automated software showed 12 mL of Tmax >6 s of

hypoperfusion in the left MCA region, which matched the lesion side. Because the ischemic core calculated by an apparent diffusion coefficient (ADC) $<620/10^{-3} \text{ mm}^2/\text{s}$ was not present, this case was diagnosed as DWI-negative DWI-PWI-mismatched AIS (Fig. 1d). Carotid vascular ultrasound showed no stenosis in the bilateral common carotid artery or internal carotid artery. We diagnosed her as AIS, and intravenous rt-PA therapy was administered 22 min after entering the MRI suite. She responded well to the reperfusion therapy, and her NIHSS was 0 after leaving the MRI suite. No further deterioration of neurological signs was observed during her admission. A FLAIR scan on the 9th day showed an ischemic change in the same lesion as the perfusion abnormality. This area was also identical to the obstructed left MCA seen on MRA. Transthoracic echocardiography did not reveal any apparent cardiac dysfunction or intracardiac thrombus. Nonvalvular atrial fibrillation was observed on day 2 of admission, and we diagnosed her stroke subtype as a cardiogenic cerebral embolism. Direct oral anticoagulant (dabigatran 300 mg/day) was prescribed at the time she was discharged to her home.

Case 2

An 88-year-old man visited the emergency room with complaints of minor unilateral spatial neglect. He had a history of hypertension and type 2 diabetes mellitus from the age of 87. The onset of symptoms was 70 min prior to presentation to the emergency room. His neurological findings confirmed minor unilateral spatial neglect, right conjugate deviation of the eyes, and dysarthria. No obvious paralysis or sensory disturbances were found. Deep tendon reflex was normal, and no pathological reflex was observed. His NIHSS was 4. His baseline MRI revealed no obvious high signal in DWI (Fig. 2a). FLAIR confirmed FLAIR vessel hyperintensities in the right MCA (Fig. 2b). MRA showed partial obstruction in the distal part of the right MCA. PWI was additionally performed and showed 60 mL of Tmax $>6 \text{ s}$ of hypoperfusion in the right MCA region, which matched the lesion side. Because the ischemic core was not obvious, this case was also diagnosed as DWI-negative DWI-PWI-mismatched AIS (Fig. 2d). Carotid vascular ultrasound showed no stenosis in the bilateral common carotid artery or internal carotid artery. He was diagnosed as AIS, and intravenous rt-PA therapy was administered 20 min after his arrival (90 min after onset). He responded well to the reperfusion therapy, and his NIHSS was 0 after 24 h. No further deterioration of neurological signs was observed during his admission. Transthoracic echocardiography did not reveal any apparent cardiac dysfunction or intracardiac thrombus. CT angiography (CTA) showed 75% stenosis in the right M1 branch (Fig. 2c), and his stroke subtype was diagnosed as an atherothrombotic brain infarction. Oral antiplatelet therapy (clopidogrel 75 mg/day) was prescribed at discharge.

Discussion

Intravenous rt-PA for AIS is an evidence-based, thrombolytic therapy as demonstrated by the NINDS rt-PA Stroke Study in 1995 [3]. Although the dosage differs in different countries (0.9 mg/kg in the United States and Europe Union vs. 0.6 mg/kg in Japan), rt-PA was approved in Japan in 2005. The time window was expanded to 4.5 h after symptom onset in 2012 [2], and the average usage of intravenous rt-PA is approximately 5–7% in Japan of all suspected stroke cases [4]. Among all subtypes of stroke, especially cardiogenic cerebral embolism can result as a high in-hospital mortality. Deteriorated level of consciousness, limb weakness, presence of congestive heart failure, male gender, and age were independent prognostic factors of in-hospital mortality in the predictive model from a previous report in patients with

cardioembolic stroke [5]. Therefore, accurate diagnosis and early treatment is required in hyperacute stroke regarding the subtypes of stroke.

MRI is widely used for diagnosing AIS in Japan. The Organization for Economic Co-operation and Development (OECD) reported in 2016 that MRI was performed at a rate of 52 per 1 million individuals in Japan, which is 3.7 times higher than the OECD's world average. This means that Japan is the most prevalent MRI-installed country among all other countries and has easy access to MRI 24/7. As a clinical advantage compared to CT scans, DWI can visualize ischemic lesions within 30 min at minimum, and DWI is a standard imaging tool in Japan for AIS in many institutions. Clinical limitations of DWI include contraindications such as a heart pacemaker, patients with severe claustrophobia, scans that are performed too early after onset and only show blurry changes in the ADC, and a possible lack of sensitivity for detecting an ischemic lesion. In our cases, the times from symptom onset to imaging were 58 and 90 min, which may not be enough time to reveal the ischemic core with ADC changes.

Recently, relative assessment of cerebral perfusion hemodynamics in real time using perfusion imaging has become possible in clinical practice within a few minutes by using mismatch software. By looking at the difference between the irreversible ischemic core and the reversible penumbra (DWI-PWI mismatch) [6], the potential for expanding time windows and a higher reperfusion rate after therapy has been reported [7–9]. In 2018, Guidelines for the Early Management of Patients with Acute Ischemic Stroke were published by the American Heart Association/American Stroke Association [10]. Two large trials used perfusion mismatch/ischemic core calculating software [11] and showed the efficacy of patient selection in a late time window who responded well to endovascular treatment (EVT). Using this multimodal imaging, the time window has expanded to 24 h with class I evidence. The EXTEND trial is now ongoing and aiming for a time window of 4.5–9 h for intravenous rt-PA using DWI-PWI mismatch [12]. However, the indication for multimodal imaging for an early time window in AIS still needs to be clarified.

The advantages and disadvantages of multimodal imaging in early time window have been discussed and are reflected in recent AHA guidelines. Time-consuming imaging is not recommended for the hazard of slowing down reperfusion therapy; hence, multimodal CT and MRI (including perfusion imaging) are not recommended in these circumstances. Alternatively, since MRI scan is achievable in many institutions for 24/7 in Japan, few institutions give intravenous rt-PA just only with CT scan, which is often followed by MRI/MRA. One reason for this is that vessel imaging modality may differ in Japan. When further vessel imaging such as CTA is needed to be assessed for endovascular therapy candidates, CTA needs to be strictly consented in Japan along with serum creatine concentration, which is time-consuming. On the other hand, recent AHA guidelines have recommended to obtain CTA without consent if no history of renal impairment exists from the fact that risk of contrast-induced nephropathy secondary to CTA imaging is relatively low. This leads MRI as a first-choice modality in Japan in order to assess the vessel by MRA after ischemic core assessment.

In our cases, although the neurologic symptoms were obvious, a high DWI signal was not clear, and occlusion/stenosis of the main artery was also not obvious. Therefore, considering the time-consuming nature of imaging diagnosis, the early edition of the 2018 AHA/ASA guideline stipulated that multimodal imaging was “not recommended” within 6 h of onset in patients. In fact, in the sub-analysis of the SWIFT-PRIME study, which looked at the workflow, time course, and effect of EVT using CT/MR perfusion images, the median time from onset to qualifying imaging was 134.5 min [1]. In the ESCAPE trial, which used only CT [13], the time was 135 min. From the data above, our AIS patients underwent imaging approximately 20 min within symptom onset, and the diagnosis was difficult with routinely used Alberta Stroke

Program Early CT Score (ASPECTS) or DWI. Neurological signs and PWI were the only factors that confirmed their diagnoses. Fortunately, the recent AHA/ASA guideline has removed the “multimodal imaging as harm” part due to the rate of a high modified Rankin scale (mRS) at 90 days after the use of multimodal imaging as shown in clinical trials. For example, EXTEND-IA (100% CT perfusion; EVT [71%] vs. control [40%] for frequency of mRS 0–2 at 90 days) compared to MR CLEAN (only CT and DSA; EVT [33%] vs. control [19%] for frequency of mRS 0–2 at 90 days) almost doubled the good outcomes in mRS.

Our cases were atypical for stroke since motor symptoms were not observed, and the chance of a stroke mimic remained during the examination. Acute imaging such as DWI and MRA sometimes cannot diagnose AIS cases, and clinicians cannot be positive that performing reperfusion therapy is appropriate for such atypical stroke cases [14]. Adding multimodal imaging such as perfusion studies may provide confidence about the diagnosis and treatment plan for patients. We analyzed MR perfusion images a posteriori using automated software (RAPID, iSchemaView, Menlo Park, CA, USA, version 4.6). In a previous supporting report [15], the analysis time due to RAPID does not appear to create a difference in treatment time. Our hospital displays the perfusion mismatch map in about 3–5 min, and therefore, adding multimodal imaging analysis does not delay the treatment itself. Acute reperfusion therapy in AIS patients has progressed from conventional time-based therapy to tissue-based therapy, and the early and late onset time windows have been expanded. Although “time is brain,” even in the acute phase, we suggest that adding multimodal imaging may identify more patients that could benefit from intravenous rt-PA if the diagnosis was unsure.

Conclusion

We experienced two cases in which rt-PA therapy was effective after performing PWI in patients with AIS. We suggest that MR perfusion imaging may be useful for excluding stroke mimic patients and has a potential to maximize the population who can achieve reperfusion therapy in difficult cases.

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Statement of Ethics

For these patients, no investigations or interventions were performed outside routine clinical care. Written informed consent was obtained from the patients for the publication of these case reports.

Disclosure Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

Dr. T.M. was involved in the workup of patient case 1, planning and conducting investigations, and providing clinical care. Dr. M.I., Dr. K.I., and Dr. K.M. performed these roles for patient case 2. Dr. K.Y. planned to report these cases, wrote the initial manuscript, reviewed and edited the manuscript, and approved the manuscript for final submission, under the guidance of Dr. M.I. Dr. K.T. and Dr. M.K. assisted with planning clinical investigations, reviewed the manuscript, collected data for the manuscript, and approved the manuscript for submission.

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Fig. 1. Case 1. MRI-DWI (a) at arrival showed no high signal area. MRI-FLAIR (b) at arrival showed a hyperintense vessel sign in the left middle cerebral artery region (arrowheads). MRA (c) at arrival showed blood vessel disruption in the left middle cerebral artery M2 (arrow). Perfusion deficit in the mismatch map. Prolongation was seen in Tmax > 6.0 s in the left MCA lesion. The DWI-PWI mismatch was 12 mL (d).

Fig. 2. Case 2. MRI-DWI (a) at arrival showed no high signal area. MRI-FLAIR (b) at arrival showed a hyperintense vessel sign in the left middle cerebral artery region (arrowheads). CTA (c) showed stenosis in the right MCA (arrow). MRI RAPID showed a region with $T_{max} > 6.0$ s in the right MCA region. The DWI-PWI mismatch was 60 mL (d).