

Case report

Thrombolytic therapy in total mismatch with severe stroke after acute MCA-occlusion and negative DWI

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1. Introduction

Total mismatch is a recently described magnetic resonance imaging (MRI) pattern in acute stroke patients with no signal changes in diffusion weighted images (DWI) and extensive hypoperfusion on perfusion weighted images (PWI). The prognostic value and importance for treatment decision based on this finding in MRI have recently been controversially discussed in patients with minor stroke [1,2]. Here we report a case of a 98-year-old woman that presented with severe stroke and total mismatch in the left middle cerebral artery (MCA) territory in MRI scan and an occlusion of the proximal MCA (M1) in time-of flight MR angiography (TOF-MRA). The patient was treated with systemic thrombolysis followed by complete remission of neurological symptoms and remaining negative DWI in post treatment MRI. We discuss the possible pathophysiological background of this phenomena and its impact on tailoring therapeutic strategies in patients with relative contraindications to thrombolytic therapy.

2. Case report

A 98-year-old woman was admitted to our hospital 50 min after sudden onset of global aphasia and right-sided sensorimotoric hemisyndrome (National Institutes of Health Stroke Scale (NIHSS)=13; modified Rankin Scale (mRS) before incident=0). 63 min after symptom onset a 3 T MRI was performed. Despite the serious neurological deficit, DWI images showed no restrictions. However, PWI displayed an extensive hypoperfusion in the left middle cerebral artery territory with corresponding M1 occlusion in the TOF-MRA (Fig. 1A).

Acute intracranial haemorrhage or microbleeds could be excluded in T2*. Despite the great age of 98 years a systemic thrombolysis as an individual treatment attempt was performed due to the severe neurological deficit and pre-stroke mRS of 0 in combination with a total mismatch and M1-occlusion in MRI and MRA. After exclusion of other contraindications recombinant tissue plasminogen activator (rt-PA) was administered with a dose of 0.9 mg/kg intravenously 85 min after stroke onset. Concurrent lessening of neurological symptoms could be observed. During thrombolysis a transcranial duplex examination was performed which yielded a recanalization of left M1. 2 h after therapy onset neurological symptoms were completely resolved (NIHSS = 0). An additional MRI scan at that time still showed no restrictions on DWI images, but a clear decline of perfusion deficits with small persistent hypoperfusion in the left central MCA territory. MRA showed a complete

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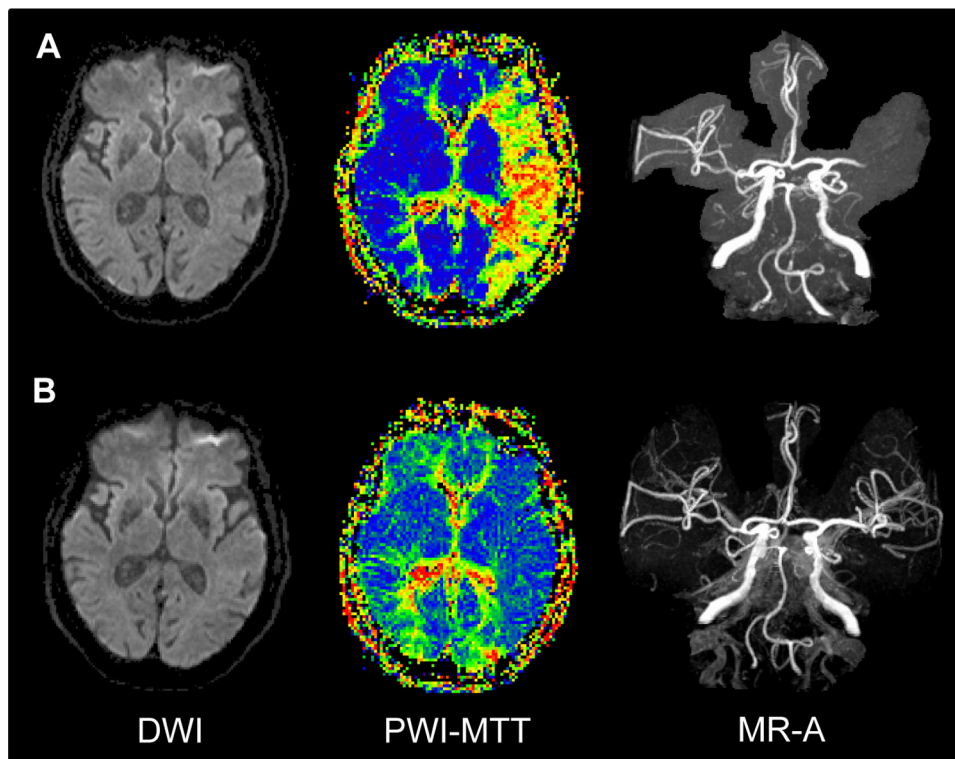


Fig. 1. (A) Baseline MRI (DWI, MTT, TOF-MRA) showing left MCA M1 occlusion and extensive perfusion deficit with negative DWI. (B) MRI 2 h after systemic thrombolytic therapy (DWI, PWI-MTT, TOF-MRA) reveals recanalization of left MCA M1 with nearly complete reperfusion and still no signal changes in DWI.

recanalization of M1 (Fig. 1B). No signs of haemorrhagic transformation were noted on T2* images.

Despite the good neurological outcome the patient suffered a heart attack and had to be resuscitated one day later. The patient was transferred to the intensive care unit and died 12 days later due to cardiac failure. Hence no further follow up MRI could be performed.

3. Discussion

We report a case of a 98-year-old woman with a severe stroke and total mismatch in MRI (no signal changes in DWI but extensive PWI deficit of nearly the whole left MCA-territory) who was treated with systemic thrombolytic therapy. Follow-up MRI 2 h after thrombolytic therapy (3 and a half hours after symptom onset) revealed persistent negative DWI but diminishing hypoperfusion and consecutive recanalization of preceding MCA occlusion. Correspondingly all neurological symptoms had resolved at that time.

DWI is a sensitive and early marker of cytotoxic edema in cerebral ischaemia. Negative DWI is mostly found in brain stem infarction or lacunar syndromes in patients with mild stroke symptoms [3]. Territorial stroke caused by occlusion of M1 with severe neurological deficits and initial negative DWI is rare. According to the severe neurological symptoms, M1 occlusion and extensive perfusion deficit in the presented case we would have expected a signal change in DWI 50 min after stroke onset.

Recently three patients with fluctuating symptoms (varying NIHSS from 0 to 10) and a total mismatch in MRI who had a favourable outcome after intravenous thrombolytic therapy were reported. The authors concluded that PWI can facilitate treatment decisions in unstable cases with negative DWI.

They hypothesized that negative DWI in these patients could be explained through a moderate hypoperfusion not severe enough to produce a diffusion lesion [2]. At least two of the reported patients

showed an extensive hypoperfusion in more than 2/3 of the MCA territory, which does not necessarily correspond to a moderate hypoperfusion. Unfortunately the authors did only state that time between symptom onset and MRI was less than 6 h and did not give the exact time. Total mismatch could be explained by a reduction in cortical blood flow that is caused in our case by MCA-occlusion and possibly in part compensated by increase of collateral blood flow. The reduction of cortical blood flow could be severe enough to reach the threshold for causing neural dysfunction and signal changes in PWI but too slight to cause major energy failure with consequent DWI changes especially in sequences obtained close by symptom onset.

Another case series reported four patients with minor stroke, middle cerebral artery occlusion and total mismatch who had a spontaneous recovery of ischaemic symptoms without thrombolytic therapy. Follow-up imaging 96 h later revealed new lesions in DWI and recanalization in all patients. In contrary to Cho et al. the authors assumed that total mismatch represents a surrogate marker for favourable outcome without the necessity of thrombolytic therapy [1].

Although unproven, it is widely assumed that the area of PWI–DWI mismatch, characterized by a larger region of hypoperfusion than the region of diffusion abnormality, represents, at least in part, remaining salvageable tissue (the so called penumbra) that could be saved by recanalizing therapy. The mismatch concept might help for selection of patients for delayed treatment who may benefit from thrombolytic therapy beyond 3 or 4.5 h.

As unthresholded visual PWI/DWI mismatch overestimates tissue at risk, it is a major challenge to define which single or combined perfusion parameter threshold allows best to distinguish between benign oligemia and penumbra to give a reliable estimate of tissue fate. Using the perfusion parameter T_{max} , a threshold between 4 and 6 s appeared in a retrospective analysis optimal for early identification of critically hypoperfused tissue [4]. Fig. 2 shows the

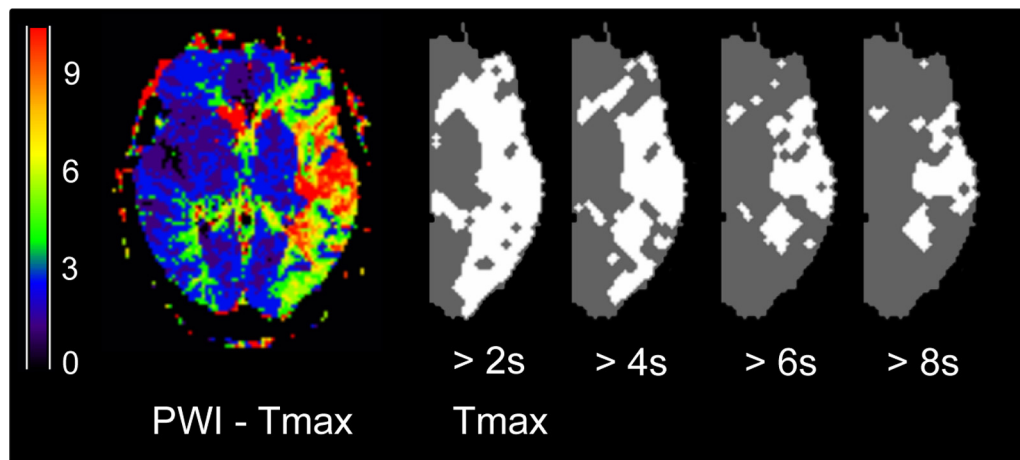


Fig. 2. Illustration of PWI deficits according to initial T_{max} maps obtained 63 min after stroke onset. Different T_{max} delays (>2 s, >4 s, >6 s, >8 s) were generated by thresholding the respective images. The amount of critical hypoperfused tissue decreases with prolonged delay but is still present even at a threshold >8 s.

T_{max} perfusion maps of the presented patient with still extended PWI deficits at T_{max} thresholds between 4 and 6 s emphasizing the urgency of recanalizing therapy.

Based on the presented data by Kim et al. [1] it is not possible to conclude that the reported four patients would have had a favourable outcome in case of no recanalization. Due to the low number of patients it remains unclear if spontaneous recanalization is associated with total mismatch or occurred incidentally in these four cases.

As chances of recanalization are improved through treatment with rt-PA the clinical course of these patients argues rather for an early thrombolytic therapy in patients with total mismatch with a high fraction of tissue at risk and clinical symptoms of (minor) stroke. Not treating these patients with a dramatic perfusion defect and verified vessel occlusion would leave them at risk for permanent severe neurological deficits. The good neurological outcome in the presented patient with a short delay from symptom onset to treatment underlines the importance of rapid procedures in acute stroke patients.

As prevailing license criteria for thrombolytic therapy with rt-PA are restricted to patients under the age of 80 the advanced age of the presented patient could have argued against thrombolytic therapy. Until recently no randomized controlled trial assessed the benefit/risk ratio for thrombolytic therapy in stroke patients at a great age. However, the just published IST-3 trial could show that treatment with rt-PA within 6 h after stroke onset also improves functional outcome in elderly patients and may extend the use of thrombolytic therapy in this population [5].

Our case shows that total mismatch might also be a positive predictor for successful thrombolysis in patients who are more severely affected than reported before (NIHSS 13). Unfortunately the patient suffered of cardiac complications that were most likely not associated with stroke treatment, which made additional evaluation of her further neurological and functional outcome impossible. It cannot be excluded that the myocardial infarction was a consequence of a detached pre-existing intracardiac

thrombus or a prothrombotic state following rt-PA treatment. However, in contrast to rt-PA treated coronary patients the use of antiplatelet strategies or anticoagulation as adjunctive therapy should be avoided in rt-PA treated stroke patients during the first 24 h after thrombolysis due to the extra risk of intracerebral haemorrhage.

4. Conclusion

Total DWI–PWI mismatch is an interesting imaging phenomenon, whose impact and underlying pathophysiology are not completely understood. The finding of total mismatch in MRI might help planning therapeutic strategies especially in patients with relative contraindication to thrombolysis such as high age as in the presented case.

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