

Case Report

Late Resolution of Diffusion-Weighted MRI Changes in a Patient With Prolonged Reversible Ischemic Neurological Deficit After Thrombolytic Therapy

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Background—Reduced apparent diffusion coefficients (ADCs) correlate with cerebral ischemia. The combination of ADC with techniques to measure cerebral perfusion may help to assess the effect of treatment.

Case Description—The authors describe a patient who experienced an acute stroke with hemianopia, consequently treated with intravenous recombinant tissue plasminogen activator. Positron emission tomographic imaging and MRI, including diffusion-weighted MRI, were performed during and shortly after treatment with recombinant tissue plasminogen activator and 34 to 35 hours later. Cerebral perfusion of the left occipital region was reduced to 74%. Diffusion-weighted MRI detected a territory of restricted water movement in the corresponding area. Further magnetic resonance sequences did not show any pathologies. In follow-up, positron emission tomography demonstrated reperfusion. The volume of diffusion and ADC abnormalities detected by MRI decreased markedly. A few hours later, the patient recovered completely. A third MRI examination 10 days later showed normal findings.

Conclusions—In a patient with prolonged reversible ischemic neurological deficit, resolution of early diffusion changes corresponded to cerebral reperfusion and to the recovery of clinical symptoms. (*Stroke*. 2000;31:2715-2718.)

Key Words: magnetic resonance imaging, diffusion-weighted ■ stroke management ■ thrombolytic therapy
■ tomography, emission computed

Diffusion-weighted MRI (DW-MRI) is able to detect cerebral ischemia within minutes after the onset of stroke.¹ The combination of DW-MRI with methods to assess cerebral perfusion provides additional information. Thus, the mismatch of diffusion and perfusion abnormalities is presumed to represent tissue at risk.²⁻⁵ The target of stroke therapy is to save this tissue.

There is some evidence in experimental⁶ and in human stroke that abnormalities in DW-MRI are reversible. In patients with transient ischemic attack (TIA)^{7,8} and after thrombolysis,⁹⁻¹¹ the resolution of diffusion changes has been observed. Thus, apparent diffusion coefficient (ADC) reduction is not equivalent to irreversible ischemia. In well-defined circumstances of experimental stroke, an ADC threshold that allowed the differentiation of core and penumbra areas of infarcted tissue was set up.¹² The reversibility of DW-MRI is of potential clinical implication in the monitoring of stroke treatment.

We present a patient with resolution of diffusion changes as late as 35 hours after stroke onset and reperfusion documented by positron emission tomography (PET) after recombinant tissue plasminogen activator (rtPA) thrombolysis.

Case Report

A 56-year-old man presented with hemianopia of the left upper quadrant. Symptoms had begun 90 minutes before admission. Previous medical history was uneventful.

A native CT scan performed immediately after admission to the hospital was unremarkable. After informed consent of the patient, 0.9 mg/kg rtPA (alteplase [Actilyse], Thomae) was administered intravenously for 60 minutes (10% bolus, 90% continuously) beginning 130 minutes after the onset of stroke.

Cerebral blood flow (CBF) was measured on an ECAT EXACT HR PET scanner (Siemens/CTI) in a 2D data acquisition mode providing 47 contiguous 3-mm slices at 5-mm full width at half maximum in-plane reconstructed resolution. CBF was measured 140 minutes and 34 hours after the onset of symptoms according to the [¹⁵O]H₂O intravenous bolus method,¹³ with 60 mCi used for each study. All voxels within the ipsilateral hemisphere below average [¹⁵O]H₂O distribution of the contralateral hemisphere were considered hypoperfused. The hypoperfused volume was determined by thresholding, and absolute CBF (in milliliters per 100 g per minute) within this hypoperfused area was calculated as described by Löttgen et al.¹⁴

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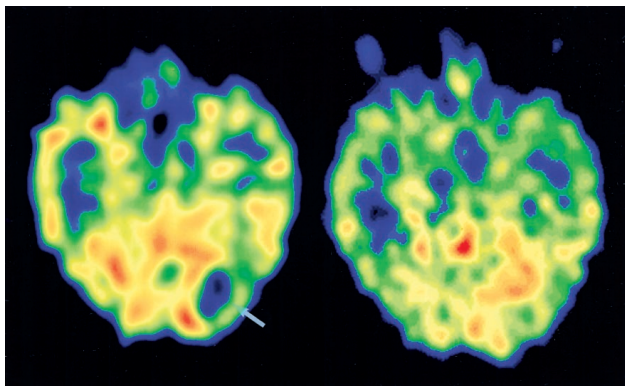


Figure 1. [^{15}O]H $_2\text{O}$ PET images 2.5 hours (left) and 34 hours (right) after onset of hemianopia of left upper quadrant. Perfusion deficit of left side optic radiation (arrow) was completely resolved after thrombolytic therapy.

MRI (Gyrosan ACS NT, Philips Medical Systems) was performed 4.5 hours and 35 hours after the onset of stroke. The MRI protocol included T1- and T2-weighted spin-echo images, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted multishot echo-planar imaging (DW-MRI, b factors 0 and 750 s/mm 2 , diffusion gradients in x, y, and z directions) with cardiac triggering and navigator echo-based motion correction. ADC maps were calculated on a pixel-by-pixel basis.

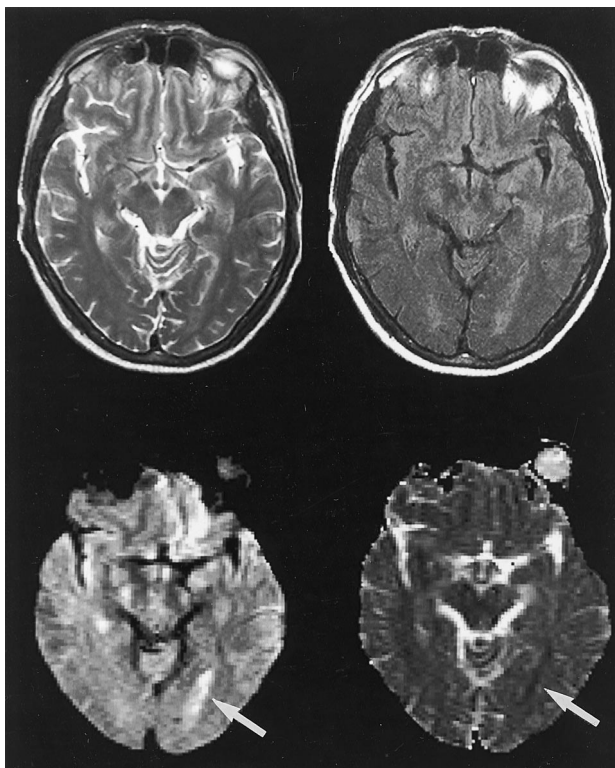


Figure 2. T2-weighted TSE image (top left), FLAIR image (top right), DW-MRI (bottom left), and corresponding ADC map (bottom right) 4.5 hours after onset of symptoms. T2-weighted TSE and FLAIR sequences are unremarkable (in T2-weighted image, part of posterior horn of left ventricle is seen). In DW-MRI, left side optic radiation is hyperintense (arrow), indicating cellular edema in acute ischemia. ADC is reduced (arrows).

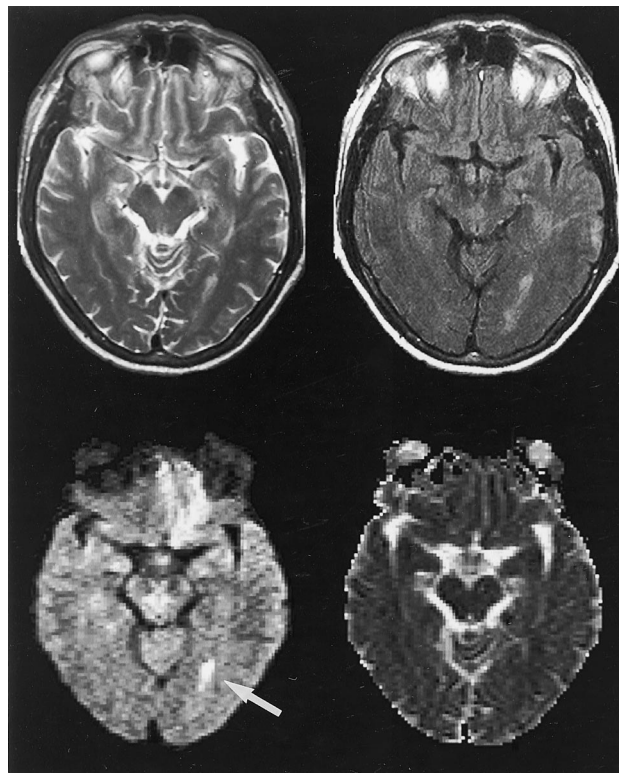


Figure 3. MRI sequences are the same as in Figure 2. After rtPA treatment and successful reperfusion, the area of hyperintensity in DW-MRI (arrow) has diminished 35 hours after onset of symptoms. Slight hyperintensity of optic radiation in T2-weighted and FLAIR images presumably indicates vasogenic edema. There is no visible interhemispheric ADC difference of optic radiation.

The DW-MRI volume was measured by 2 investigators by outlining regions of abnormality by hand. ADC volume was determined by an automatic threshold method. The threshold was defined as the mean isotropic ADC of the identical region of the contralateral side reduced by 2 SD (ie, 95% CI). In addition, the mean value of the isotropic ADC was measured in an area corresponding to the diffusion-positive region and compared with the identical region of the contralateral hemisphere.

At the time of the first PET examination, the volume of hypoperfusion in the left occipital region was 14.5 cm 3 (Figure 1). [^{15}O]H $_2\text{O}$ uptake was reduced to $74 \pm 9\%$ (minimum 50%, maximum 89%) in that region. The median value of CBF was 22.5 mL/100 g per minute (minimum 12 mL/100 g per minute, maximum 30 mL/100 g per minute).

At 4.5 hours, the volume of increased signal intensity in the left occipital region in DW-MRI was 1.3 cm 3 . The ADC of the diffusion-positive lesion was reduced to 78.6% of the contralateral site (volume of reduced ADC 0.5 cm 3). All other imaging sequences were unremarkable (Figure 2).

At 34 hours, perfusion was normal by PET (Figure 1). The volume of reduced diffusion was decreased to 0.75 cm 3 . The ADC was reduced to 91.2% (ADC lesion volume 0.19 cm 3). In FLAIR and T2-weighted images, a slight signal hyperintensity was detectable in the area of the optic radiation (Figure 3).

Summary of Results

	Early Measurement	Late Measurement
PET		
Time of measurement after onset of stroke	2.3 h	34 h
Volume of CBF reduction	14.5 cm ³	No reduction (normal)
Degree of CBF reduction in volume of reduced perfusion	74±9%	No reduction (normal)
Median absolute CBF in volume of reduced perfusion	22.5 mL · 100 g ⁻¹ · min ⁻¹	No reduction (normal)
Median absolute CBF in region with abnormal diffusion	16.5 mL · 100 g ⁻¹ · min ⁻¹	Not applicable
MRI		
Time of measurement after onset of stroke	4.5 h	35 h
Volume of DW-MRI abnormality	1.3 cm ³	0.75 cm ³
Volume of ADC reduction (95% CI)	0.5 cm ³	0.19 cm ³
Degree of ADC reduction in area of abnormal DW-MRI	78.6±6.4%	91.2±5.2%
Hyperintensity in FLAIR	No	Yes
Hyperintensity in T2-weighted spin echo	No	Yes

The patient recovered completely a few hours after the second MRI examination. A third MRI 10 days later showed normal intensity patterns in all sequences including DW-MRI.

All results are summarized in detail in the Table.

Discussion

Two mechanisms are responsible for recovery of reduced ADC after stroke. The first is a pseudonormalization, indicating loss of cell membrane integrity with the development of tissue necrosis. The duration of the ADC reduction in humans is typically 5 to 10 days.^{15,16} However, up to 42 days (until pseudonormalization), reduced ADCs have been observed.¹⁷

The second possible reason for ADC normalization is tissue recovery. In animal experiments of cerebral ischemia, the correlation of reperfusion and the recovery of ADC and ATP and of tissue pH have been documented.^{6,18} In humans, reversibility of diffusion changes after an ischemic event has been documented in patients with TIA^{7,8} and in patients after thrombolysis.^{9,11} Thus, the results of the literature as well as our case report support the hypothesis that diffusion-positive MRI lesions do not invariably represent irreversible ischemia.

In our case study, we observed a vast difference between the large volume of the perfusion deficit and the small volume of the diffusion abnormality. The relationship between perfusion and diffusion abnormalities in humans after stroke is under intensive investigation.²⁻⁵ Typically, the region with reduced perfusion is larger than the DW-MRI lesion during the first hours of stroke evolution, as it was in our case study.^{17,19,20} This mismatched region represents "tissue at risk" and is therefore regarded as potentially salvageable brain tissue, depending on the degree of hypoperfusion.² In our case study, both diffusion and perfusion normalized after thrombolytic therapy, which supports the importance of the region mismatch as a prognostic factor early in the course of ischemia. The relatively small volume of diffusion abnormality and ADC reduction is probably

explained by the fact that the degree of hypoperfusion was not severe (regional relative CBF 50% to 89%). Moreover, in contrast to DW-MRI, calculated ADC is not sensitive to T2 prolongation. The limitation in our case study is the time interval of ≈2 hours between the first PET and MRI examination. Furthermore, rtPA was started before the PET examination. Therefore, the perfusion status was probably different 2 hours later, when MRI was performed. It is remarkable that the diffusion lesion volume was similar to that in data of patients with TIA.^{7,8} In patients with completed stroke, the diffusion volume is usually larger.⁹

Late resolution of diffusion changes as in our case study has not been reported in the literature so far. Kidwell et al⁷ observed resolution of diffusion changes detected at a mean time of 12.7 hours after the onset of symptoms in patients with TIA. However, the resolution of DW-MRI changes does not necessarily imply a favorable clinical outcome. In clinical and experimental studies,^{9,21} a second deterioration of initially improved ADC after thrombolysis has been noticed. Even in patients with TIA, who presented with diffusion-positive lesions, 50% of these lesions developed to infarction.⁷ In our case study, we did not observe this phenomenon.

The combination of DW-MRI and PET holds the possibility of correlating diffusion changes with quantitative CBF data and therefore may help us to understand the pathophysiology of stroke. However, in clinical practice, logistical problems may be time-consuming. A good alternative to PET is perfusion-weighted MRI, which is easy to combine with DW-MRI without loss of time.

In conclusion, we report for the first time the resolution of diffusion abnormalities in a patient with prolonged reversible ischemic neurological deficit after thrombolysis. The combination of PET and DW-MRI, including ADC mapping, proved to be helpful in monitoring the response to thrombolytic therapy.

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