Original Article

False-negative and False-positive Diffusion-weighted MR Findings in Acute Ischemic Stroke and Stroke-like Episodes

Shuzo Shintani¹, Hiroaki Yokote¹, Kaoru Hanabusa² and Tatsuo Shiigai³

Departments of ¹Neurology, ²Diagnostic Radiology, and ³Internal Medicine, Toride Kyodo General Hospital, Ibaraki, Japan

Abstract

Background: Diffusion-weighted magnetic resonance (MR) imaging (DWI) is an excellent examination for detecting acute ischemic stroke, but false-negative cases have been reported recently.

Patients and Methods: Since the present MR scanner (1.5-T, Siemens Symphony) was introduced to our hospital, a prospective study was designed in the Departments of Neurology and Radiology to evaluate the DWI findings in patients tentatively diagnosed to have an acute infarction and in those with stroke-like episodes. During the 31 months between June 2000 and December 2002, 572 consecutive patients with acute cerebral infarction or presenting conditions mimicking ischemic stroke, including transient ischemic attack (TIA), sudden-onset isolated vertigo, and loss of consciousness (LOC) with or without seizure, underwent DWI.

Results: Four of 366 patients with a cerebral infarction (1.1%) had false-negative DWI in the acute stage, and 10 of 206 patients with conditions mimicking ischemic stroke (4.9%) had false-positive DWI in the acute stage. Of these 10 patients, there were five cases with TIA, four with sudden-onset isolated vertigo, and 1 with LOC with seizure. Sensitivity and specificity values were 98.9% and 97.6%, respectively, when DWIs were performed to diagnose acute cerebral infarction.

Conclusion: DWI rarely fails to detect an acute-stage cerebral infarction, but further confirmatory measures may be necessary when there is a negative examination using a clinical or computed tomographic diagnosis to the contrary.

Key words: acute ischemic stroke, stroke-like episode, magnetic resonance imaging, diffusion-weighted imaging, ischemic penumbra

Correspondence to: Shuzo Shintani
Department of Neurology,
Toride Kyodo General Hospital,
2-1-1 Hongoh, Toride City, Ibaraki 302-0022, Japan
E-mail: dw4s-sntn@asahi-net.or.jp

Introduction

Diffusion-weighted magnetic resonance (MR) imaging (DWI) is much more sensitive than conventional T2-weighted MR imaging or computed tomography (CT) for detecting early changes associated with hyperacute ischemic stroke; the reported sensitivity approaches 100%. Recently, however, several false-negative cases have been reported^{1–3}. In 1999, Ay et al. identified 27 cases among 782 consecutive patients who presented with stroke-like neurologic deficits but DWI in the area relevant to the symptoms was found to be normal¹. In the same year, Wang et al. reported on two patients with large acute cortical infarcts but negative DWI and discussed possible mechanisms². In 2000, Oppenheim et al. described false-negative DWI in eight of their acute stroke cases (5.8%), including five with brain-stem infarcts and three with cerebral lesions³.

We report on the prevalence of false-negative acute-stage DWI studies in patients with persistent neurologic deficits due to ischemic stroke, and the putative causes why DWI initially missed the lesion will be discussed.

Methods and Patients

Methods

The present MR scanner (1.5-T, Siemens Symphony) has been in use in our hospital since June 2000. Multi-slice whole-brain DWI was performed in patients provisionally diagnosed to have acute ischemic stroke or conditions mimicking ischemic stroke. DWI were obtained in the axial plane by combining a single-shot spin-echo (SE)-type echo planar imaging (EPI) sequence and additional motion probing gradient (MPG) pulses in three orthogonal axes. Imaging parameters were as follows: echo time (TE) 154 msec; matrix, 128×128; field of view (FOV), 23×23cm; slice thickness, 5mm; and intersection gap, 1.5mm. The b-values were 0 and 1000 sec/mm².

Other routine MRI sequences included the following: axial spin-echo (SE) T1-weighted images

(TR/TE=650/16, matrix 256×192, FOV=23×23cm, slice thickness=5mm, 1.5-mm gap, 1 signal acquisition); axial Turbo spin echo (TSE) T2-weighted images (TR/TE=4500/98, matrix 256×192, FOV=23×23cm, slice thickness=5mm, 1.5-mm gap, 1 signal acquisition). Each imaging series consisted of 20 sequential sections of the entire brain.

Patients

At our hospital, it is routine to perform brain CT on admission to the emergency room (ER) as a first-line diagnostic evaluation for patients with sudden-onset neurologic deficits. These patients have, by definition, positive scores on the National Institute of Health Stroke Scale (NIHSS)⁴⁾ on admission. Those without neurologic deficits on admission have had positive NIHSS scores when they first developed the attacks prior to the present admission. When CT reveals no abnormalities, MR studies are recommended by an ER physician. DWI is another auxiliary choice to reliably detect ischemic lesions in an extremely acute stage.

Following the introduction of Siemens Symphony, a prospective study was designed in the Departments of Neurology and Radiology to evaluate the DWI findings in patients provisionally diagnosed to have acute cerebral infarction or conditions mimicking ischemic stroke since June 2000. This study was approved by the institutional review committee of the hospital and was performed between June 2000 and December 2002. The MR findings were evaluated twice, by both a registered radiologist (KH) and a neurologist (SS).

During the 31 months of the study, DWIs were performed on 572 consecutive patients with acute cerebral infarction or with conditions mimicking ischemic stroke. The former group of patients were confirmed to have positive neurologic deficits and the latter to not have neurologic deficits on admission. The latter group of patients consisted of those with transient ischemic attack (TIA), sudden-onset isolated vertigo, or loss of consciousness (LOC) with or without seizure.

Considering the diagnostic precision inherent in DWI to detect lesions of acute cerebral infarction, false-positive and false-negative cases were defined as follows: the former presented with neurologic deficits but without DWI findings and the latter presented without neurologic deficits but with DWI findings on admission.

Results

Four of 366 patients with cerebral infarction (1.1%) had false-negative DWI in the acute stage (Table 1; Figures 1 and 2). Ten of 206 patients with conditions mimicking ischemic stroke (4.9%) had false-positive

DWI in the acute stage (Table 2; Figure 3). Of these patients, there were five with TIA, four with sudden-onset isolated vertigo, and one with LOC with seizure. Sensitivity and specificity values for detecting lesions of acute cerebral infarction by DWI were 98.9% and 97.6%, respectively (Table 3).

Case Reports

Patient 1 (false-negative case, Figure 1)

A 69-year-old man with a history of hypertension and cerebral infarction 3 years prior to admission developed right hemiparesis. He had been prescribed ticlopidine 200mg daily to decrease the risk of a recurrent infarct as well as an antihypertensive drug (Table 1). On admission, his blood pressure was 166/101 mmHg, and his heart rate was 85/min with a regular rhythm. The patient was alert, and his cranial nerves were intact. He presented with right hemiparesis, together with a slight left hemiparesis remaining. Cerebellar function and deep tendon reflexes were bilaterally normal, but a positive Babinski sign was present on the right side. CT and DWI taken 10 h after the onset of symptoms showed no abnormalities except for the previous infarct, located in the right corona radiata (Figure 1). MR angiography (MRA) revealed no abnormalities in the major vessels of the brain and neck.

The right hemiparesis persisted after admission. Follow-up DWI 9 days after the onset detected a high-intense signal lesion in the left corona radiata (Figure 1).

Patient 4 (false-negative case, Figure 2)

A 94-year-old woman with a history of hypertension and transient ischemic attack (TIA) 1 year previously suddenly developed cognitive dysfunction and developed paresis of left hand. She had been prescribed ticlopidine (200mg) and aspirin (100mg) daily to reduce risk of cerebral vascular events, and also an antihypertensive drug (Table 1). On admission the blood pressure was 178/74 mmHg, and the heart rate was 88/min with a regular rhythm. She exhibited paresis of left hand, and the consciousness was not clear. She was unable to respond correctly to questions. CT and DWI performed 22 h after onset of symptoms showed no abnormalities. MRA revealed no abnormalities in major vessels of the brain or neck.

After admission she showed persistent paresis of the left hand. Follow-up DWI 2 days after onset of symptoms detected a lesion with signal hyperintensity involving the right temporal, parietal, and occipital lobes (Figure 2).

Patient 5 (false-positive case, Figure 3)

This 70-year-old male with TIA revealed no

Table 1 Findings of 4 patients with sudden neurologic deficit and negative initial findings on diffusion-weighted MR study

Case No.	Age (y) Gender	Stroke risk factor	New neurologic symptoms	History of previous cerebral infarction	Residual neurologic deficits	Prescribed drug with onset of new symptom	Initial MR Findings		Follow-up MR Findings	
							MR Latency (hr)	DWI	MR Latency (days)	DWI
1	69/M	Hypertension	Sudden R hemiparesis	(+) 3 years ago	L hemiparesis	Ticlopidine Anti-hypertensive medicine	10	Negative	9	Hyperintense signal of L corona radiata
2	77/F	Hypertension Atrial fibrillation	Sudden L hemiparesis and dysarthria	(+) 8 months ago	Amnesic aphasia	Warfarin Anti-hypertensive medicine	3.5	Negative	2	Hyperintense signal of cortex and white matter of R parietal lobe
3	53/M	Hypertension Diabetes mellitus	Sudden R hemiplegia	(+) 5 years ago	L hemiparesis	Insulin Anti-hypertensive medicine	1	Negative	2	Hyperintense signal of L medulla
4	94/F	Hypertension	Sudden L upper limb paresis and acute onset dementia	TIA 1 year ago	None	Aspirin Ticlopidine Anti-hypertensive medicine	22	Negative	2	Hyperintense signal of cortex and white matter of R temporo-parieto-occipital lobe

R : right ; L : left ; TIA : transient ischemic attack ; MR : magnetic resonance ; DWI : diffusion-weighted image ; hr : hour (s).

Figure 1 (Patient 1, false-negative case)

In a 69-year-old man with sudden onset of right hemiparesis, diffusion-weighted imaging (DWI) was negative 10 h after onset of symptoms (left) ; 9 days later (right), a lesion in the left corona radiata (arrowhead) shows a hyperintense signal.

Figure 2 (Patient 4, false-negative case)

In a 94-year-old woman with sudden onset of left upper limb paresis and acute cognitive deterioration, diffusion-weighted imaging (DWI) was negative 22 h after onset of symptoms (left) ; 2 days later (right), hyperintense signals were seen in the cortex and white matter of portions of the right temporal, parietal, and occipital lobes (arrowheads).

Table 2 Findings of 10 patients with negative neurologic deficits and positive initial findings on diffusion-weighted MR study

Case No.	Diagnosis	Age (y) Gender	New neurologic deficits on admission	Transient symptoms	Stroke risk factor	Residual neurologic deficits	Prescribed drug with onset of transient symptom	MR Latency (hr)	Intensity in ADC map
5	TIA (1-hr duration)	70/M	Negative	Left arm paresis and dysarthria	Negative	Negative	None	2	low
6	TIA (3-hr duration)	74/M	Negative	Left leg paresis	Hypertension	Negative	Anti-hypertensive medicine	48	low
7	TIA (5-hr duration)	80/F	Negative	Numbness of right arm and dysarthria	Hypertension, old cerebral infarct	Dementia	Ticlopidine, Aspirin, Anti-hypertensive medicine	185	equal
8	TIA (30-min duration)	68/M	Negative	Right arm paresis and dysarthria	Hypertension, Atrial fibrillation	Negative	Anti-hypertensive medicine	3	equal
9	TIA (10-min duration)	71/M	Negative	Right leg paresis and dysarthria	Hypertension	Negative	Anti-hypertensive medicine	15	equal
10	Sudden onset isolated vertigo	58/M	Negative	Vertigo and nystagmus	Diabetes mellitus	Negative	Anti-diabetic medicine	15	(artifact)
11	Sudden onset isolated vertigo	74/M	Negative	Vertigo	Hypertension	Negative	Anti-hypertensive medicine	170	low
12	Sudden onset isolated vertigo	80/F	Negative	Vertigo	Negative	Negative	None	16	equal
13	Sudden onset isolated vertigo	59/M	Negative	Vertigo	Hypertension, Diabetes mellitus	Negative	Anti-hypertensive medicine, Insulin	14	low
14	LOC with seizure	64/M	Negative	LOC and convulsion	Negative	Negative	None	10	low

TIA : transient ischemic attack ; LOC : loss of consciousness ; ADC : apparent diffusion coefficient ; hr : hour (s) ; min : minutes.

Figure 3 (Patient 5, false-positive case)

Diffusion-weighted imaging was positive in the acute stage in a patient with a transient ischemic attack (TIA).

neurologic deficits on admission (Table 2), but DWI showed a positive high-intensity region.

Discussion

Since 1999, there have been reports of several patients with acute cerebral infarction who had false-negative DWI¹⁻³. Ay et al. identified 27 cases among 782 consecutive patients¹. They had neurologic deficits on admission, but DWIs revealed no corresponding abnormalities. However, the final diagnosis was conditions mimicking stroke in 10 of the patients (migraine, seizures, transient global amnesia, or brain tumor) and a cerebral ischemic event in only 17 patients (2.2%). The latter included 7 patients with lacunar syndrome (including three with infarcts demonstrated subsequently) and 10 patients with hemispheric cortical syndromes (five with TIA, two with prolonged reversible deficits, and three with

Table 3 Accuracy of DWI findings of MRI in an acute stage of cerebral infarction and in a condition mimicking ischemic stroke

	Acute stage of cerebral infarction	Transient ischemic attack (TIA)	Sudden onset isolated vertigo	Loss of consciousness with or without seizure
	Positive neurological deficits when MRI was Performed on admission	Negative neurological deficits when MRI was performed on admission		
Patients with positive DWI findings in initial MRI	362	5**	4**	1**
Patients with negative DWI findings in initial MRI	4*	17	91	88

DWI : diffusion-weighted image ; *False-negative cases ; **False-positive cases ; Sensitivity=98.9% ; Specificity=97.6%.

infarction on follow-up imaging).

In that year and the following year, Wang et al. and Oppenheim et al. described false-negative DWIs in acute ischemic stroke cases and discussed possible mechanisms^{2,3}. They concluded that vertebrobasilar stroke cannot be ruled out by a negative early DWI, particularly when symptoms suggestive of this diagnosis persist.

In our four patients (Patients 1 to 4), follow-up T2-weighted images showed high intensity regions corresponding to the hyper-intense lesions in the follow-up DWIs. These positive findings in follow-up T2-weighted images in areas accounting for the neurologic deficits suggest that the patients had ischemic events.

Lesion sites varied in our four patients. We concluded that the occluded vessels were a perforating artery in the white matter of the corona radiata in patient 1 (thrombosis), a parietal branch of the right middle cerebral artery (MCA) in patient 2 with AF (embolism), a left-sided perforating artery of the medulla in patient 3 (thrombosis), and a temporoparietal branch of the right MCA in patient 4 (possible embolism). The prevalence of false-negative DWI among acute infarcts at our hospital was 1.1% (4 in 366), which is somewhat lower than previous research reporting a 2.2%¹ or 5.8%³ prevalence.

In the current study we addressed not only the false-negative rate but also the false-positive rate. The values of sensitivity and specificity were 98.9% and 97.6%, respectively, when DWIs were performed for the diagnosis of acute cerebral infarction (Table 3).

First, five patients (Patients 5 to 9) with TIA had small hyperintense signal regions in the initial DWI on admission (Table 2). Transient symptoms were ipsilateral hemiparesis with and without dysarthria and numbness of the arm. MR latencies between the onset of symptoms and MR examination varied from 2 to 185 hours. The apparent diffusion coefficient (ADC) maps showed hypo-intense signal regions in Patients 5 and 6, but iso-intense signal regions in Patients 7, 8, and 9 in the corresponding DWI positive regions.

Etiologies of these lesions have been discussed TIA-related DWI abnormalities are associated with prolonged TIA duration and disturbance of higher brain function^{5,6}. The durations of TIA symptoms in our patients varied from 10 min to 5 hr. The relatively prolonged duration (1 hr to 3 hr) in Patients 5 and 6 might have resulted in the hypo-intense signals, and the relatively short duration (10 min to 30 min) in Patients 8 and 9 might have produced the iso-intense signals in the ADC maps. However, in Patient 7 the markedly prolonged duration (5 hr) resulted in the iso-intense signals and the failure to present hypo-intense signal regions on the ADC map.

Second, four patients (Patients 10 to 13) with sudden onset isolated vertigo had tiny hyperintense signal regions in the initial DWI (Table 2). They had no ataxia, paresis, or other symptoms of brain-stem involvement on admission. MR latencies varied from 14 to 170 hours. The lesions were located in the cerebellar peduncle, the vermis, and the corpus callosum.

The ADC maps showed hypo-intense signals in Patients 11 and 13 but an iso-intense signal in Patient 12. These results were not related to the intensities and durations of their symptoms. In Patient 10, details were not evaluated by the artifacts. Those patients might have experienced ischemic stroke in the infratentorial area. Subsequent reperfusion could have resulted in these small lesions on admission.

Third, the patient (Patient 14) with LOC with seizure had a small hyperintense signal region in the temporal lobe on the initial DWI (Table 2). The ADC map revealed a hypo-intense signal in the corresponding region. He was conscious and had no neurological deficits on admission. Lansberg et al. reported that some of the MRI and CT findings during partial status epilepticus mimicked those of acute ischemic stroke⁷.

Wang et al. suggested three possible mechanisms to explain the lack of diffusion changes in the acute phase in patients eventually proven to have infarction². First, cerebral blood flow (CBF) may have been at an intermediate level, below the threshold for neuronal

dysfunction (symptom onest) but above the threshold for reduced diffusion. Second, reperfusion may have occurred, restoring the diffusion constant to normal but not preventing eventual delayed infarction. Third, a second ischemic event may have caused the eventual infarction.

To varying extents, the above three hypotheses all involve the “ischemic penumbra” concept⁸⁾. When an ischemic stroke occurs, the peripheral vessels of the lesion initially dilate to sustain blood filling. Such compensatory vasodilation occurs in regions with mild reductions in CBF, leading to an increase in collateral blood flow and maintenance of normal cerebral blood volume (CBV). However, the reduced level of CBF may not be sufficient to maintain normal electrical activity and is reflected by functional neurologic deficits. When this autoregulatory mechanism is unsuccessful because of an excessive decrease in the blood filling pressure so that CBF becomes notably and remarkably decreased in the involved area, the oxygen extraction fraction (OEF) must be increased to maintain the oxygen supply in this region⁹⁾.

This phenomenon is sometimes referred to as “misery perfusion”. It occurs in the penumbra and does not represent irreversible ischemic involvement but rather a form of vasogenic edema of the brain. However, when the OEF reaches its upper limit, the cerebral metabolic rate for oxygen (CMRO₂) begins to decrease, and subsequently, irreversible ischemic change with cytotoxic edema produces a DWI-positive area by MR¹⁰⁾. We suggest that the prolonged “penumbra” state due to unknown reasons resulted in the false-negative DWIs in this study.

Reference

- 1) Ay H, Buonanno FS, Rordorf G, *et al.* Normal diffusion-weighted MRI during stroke-like deficits. *Neurology* 1999 ; 52 : 1784–1792.
- 2) Wang PY, Barker PB, Wityk RJ, *et al.* Diffusion-negative stroke : A report of two cases. *AJNR Am J Neuroradiol* 1999 ; 20 : 1876–1880.
- 3) Oppenheim C, Stanescu R, Dormont D, *et al.* False-negative diffusion-weighted MR findings in acute ischemic stroke. *AJNR Am J Neuroradiol* 2000 ; 21 : 1434–1440.
- 4) Lyden P, Brott T, Tilley B, *et al.* Improved reliability of the NIH Stroke Scale Using Video Training. *Stroke* 1994 ; 25 : 2220–2226.
- 5) Rovira A, Rovira-Gols A, Pedraza S, *et al.* Diffusion-weighted MR imaging in the acute phase of transient ischemic attacks. *AJNR Am J Neuroradiol* 2002 ; 23 : 77–83.
- 6) Inatomi Y, Kimura K, Yonehara T, *et al.* DWI abnormalities and clinical characteristics in TIA patients. *Neurology* 2004 ; 62 : 376–380.
- 7) Lansberg MG, O'Brien MW, Norbash AM, *et al.* MRI abnormalities associated with partial status epilepticus. *Neurology* 1999 ; 52 : 1021–1027.
- 8) Hossmann K. Viability thresholds and the penumbra of focal ischemia. *Ann Neurol* 1994 ; 36 : 557–565.
- 9) Powers WJ. Cerebral hemodynamics in ischemic cerebrovascular disease. *Ann Neurol* 1991 ; 29 : 231–240.
- 10) Kelly PJ, Hedley-Whyte ET, Primavera J, *et al.* Diffusion MRI in ischemic stroke compared to pathologically verified infarction. *Neurology* 2001 ; 56 : 914–920.