# Diffusion-Weighted Imaging: Not All That Glitters Is Gold

*Archit Bhatt, MD, MPH, Amit Masih, MD, Heather F. Grothous, BA, Muhammad U. Farooq, MD, Bharath Naravetla, MD, and Mounzer Y. Kassab, MD, MA*

**Abstract:** Diffusion-weighted imaging (DWI) is a sophisticated magnetic resonance imaging (MRI) technique with rapid acquisition time and high sensitivity for depicting acute cerebral ischemia. It is currently part of the routine workup in most medical centers when ischemic stroke is in the differential diagnosis. DWI helps establish a diagnosis of acute ischemic infarct even in cases where the clinical presentation is not typical for ischemic stroke. However, contrary to popular belief, not every hyperintensity on DWI is an ischemic stroke. Consequently, DWI with high intensity signals, commonly called "positive" DWI, is sometimes misinterpreted and leads to incorrect medical management. In this report, we briefly discuss some of the essential, technical aspects of DWI and report various clinical scenarios, which may lead to "positive" DWI findings but are not ischemic strokes. Although the sensitivity of DWI for ischemic stroke is very high, the specificity is not as high, and a "positive" DWI does not exclude other diagnoses that should be considered based on each patient's clinical history and examination, and the appearance of other sequences of MRI scans.

**Key Words:** diffusion-weighted imaging, magnetic resonance imaging, stroke

**Magnetic resonance imaging (MRI) is a diagnostic tech-**<br>mique that utilizes a magnetic field to align the hydrogen  $(H)$  atoms in the studied tissue.<sup>1</sup> H nuclei, or protons, have magnetic properties that allow them to spin on an axis, known as nuclear spin, and uniformly align once placed in a large, external magnetic field. After the initial alignment has occurred within the main field, a second external magnetic field is applied at a different radiofrequency and placed perpendicular to the original magnetic field. This disrupts the initial alignment, letting the protons drift back, realign, and

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emit a radiofrequency signal that is captured by the MRI scanner. The rate of this realignment varies with the composition and type of the tissues in the body. This results in a production of a differential, tissue-specific signal on the final MRI acquisition image. Diffusion-weighted imaging (DWI) is a sensitive technique that detects the mobility of water molecules in the brain parenchymal tissue. $1-3$  By their distinctive inherent virtue, water molecules are always in random motion, which is constant in a given isotropic medium. This theory is termed the Brownian motion of water molecules. The human brain tissue is an anisotropic heterogenous environment. Movement of water molecules across the cell membranes, blood vessels, and axons is tissue specific due to the variability in type, density, and chemical composition of the tissues. Diffusion-weighted imaging is thus an extension of the original MRI technique that is achieved by combining it with two diffusion gradient pulses. This allows monitoring of the displacement of water molecules, which can be classified into three categories: free diffusion, restricted isotropic diffusion, and restricted anisotropic diffusion. Free diffusion is seen when water is displaced freely in multiple directions, such as that found in the cerebral spinal fluid. $1-3$  Restricted isotropic diffusion is found when water molecules are re-

#### Key Points

- Diffusion-weighted imaging is a widely used MRI technique with rapid acquisition time.
- A hyperintense signal on DWI is very sensitive to detect acute cerebral ischemia but is not specific, ie not every hyperintensity on DWI is an ischemic stroke.
- The most common cause of hyperintense lesions on DWI, commonly referred to as positive DWI, are ischemic strokes.
- Non-ischemic lesions that appear very bright on T2 weighted images, commonly referred to as T2 shine through, can cause a hyperintense signal on DWI.
- Apparent diffusion coefficient (ADC) mapping plays a critical role in reaching the final diagnosis; a low intensity signal on the ADC map and a high intensity signal on DWI mostly signify an ischemic infarct.

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From the Department of Neurology and Ophthalmology and Division of Cerebrovascular Disorders, Michigan State University, East Lansing, MI.

Reprint requests to Mounzer Y. Kassab, MD, MA, A-217, 138 Service Road, Clinical Center, East Lansing, MI 48824. Email: mounzer.kassab@ht.msu.edu

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stricted in motion in a certain spatial direction, which is what occurs in the case of an abscess. Restricted anisotropic diffusion occurs when a structural lesion allows and directs the water molecule displacement.

To obtain DWI, a pair of strong gradient pulses is added to the pulse sequence. The diffusion data can then be presented as signal intensity or as an image map of the apparent diffusion coefficient (ADC). Calculating the ADC requires two or more acquisitions with different diffusion weightings. A low ADC corresponds to a high signal intensity (restricted diffusion) and a high ADC to low signal intensity on diffusion-weighted images. $1-3$ 

In the setting of acute cerebral ischemia, if the cerebral blood flow is lowered to 10 mL/100 gm/min, sodium ion pump failure leads to excessive sodium in the cell, which is followed by a net movement of water from the extracellular to intracellular compartment and cytotoxic edema. Diffusion of the water molecules in the intracellular compartment is restricted by the cell membranes. The restricted diffusion results in a decreased ADC and increased signal intensity (hyperintensity) on DWI.

## Case Reports

## **Patient 1**

A 60-year-old healthy man came to the emergency department after a generalized tonic clonic seizure with focal onset at home manifesting by motor activity of the right arm and leg. The seizure was associated with postictal weakness of the right arm and right leg, confusion, and bladder incontinence. Additional history taken in the emergency department revealed that the patient was having daily morning headaches for the last 4 weeks.

On the initial clinical evaluation, the patient was drowsy, his gaze had no preference, and both pupils were equally reactive to light. There was a mild weakness of the right arm and leg.The plantar response was extensor on the right. The rest of the neurological and physical examination was unremarkable. Initial laboratory examination was normal. A computed tomography (CT) scan of the brain showed left frontoparietal hypodensity suggesting an ischemic stroke in the differential diagnosis. The patient was started and maintained on phenytoin thereafter.

Over the next 12 hours, the patient's clinical status improved back to baseline. MRI of the brain (Fig. 1, Patient 1) revealed a heterogeneously contrast enhanced mass in the left frontoparietal region suggestive of a possible primary malignant glioma. The DWI showed a bright "hyperintense" signal in the same region (see image of Patient 1 in Fig. 1). Excisional biopsy confirmed the diagnosis of a glioblastoma multiforme.

## **Patient 2**

A 55-year-old man in his usual state of health until two weeks prior to admission started to have left hemicranial headaches that were not relieved by traditional medications. He had a history of essential hypertension and was not taking anticoagulants or antiplatelets. He denied taking any illicit drugs, over-the-counter medications, or herbal remedies. On the day of admission, a brain CT scan showed left parietal lobe hemorrhage.

Initial clinical evaluation revealed normal mental status, and speech and language evaluation revealed rightleft confusion, agraphia, and acalculia. The rest of the neurological examination was normal. His blood pressure was 140/90 mm Hg in the emergency room and the basic laboratory examination, including coagulation profile, complete blood count, and comprehensive metabolic profile, were normal. The patient's urine toxicological profile was normal. The brain MRI scan (Fig. 1, Patient 2) showed intraparenchymal hemorrhage in the left parietal region with hyperintensity on DWI.

## **Patient 3**

A 64-year-old, right-handed man had a past medical history of left temporal ischemic stroke and mild residual right hemiparesis (National Institute of Health Stroke Scale [NIHSS] of 2). Two years after being clinically stable, he presented to the emergency room with an acute complaint of slurred speech, expressive aphasia, and a worsening of his right-sided weakness. The initial evaluation by the stroke team revealed an NIHSS of 12. There was no evidence of any abnormal involuntary movement and a new stroke was in the differential diagnosis. He was immediately taken to have a CT scan of the brain, computed tomography angiogram (CTA), and brain computed tomography perfusion (CTP) as part of the acute stroke work-up protocol. The CTA did not show any hemodynamic significant stenosis and the CTP revealed evidence of hyperperfusion around the area of his previous infarct in the left temporal lobe. His electroencephalography (EEG) revealed epileptiform discharges over the left temporal region. His brain MRI revealed encephalomalacia in the left temporal lobe. The left hippocampus was edematous and hyperintense on T2-weighted image (T2-WI), fluid-attenuated inversion recovery (FLAIR), and DWI (Fig. 1, Patient 3).

Intravenous (IV) lorazepam and levetiracetam 1000 mg were given and the patient was maintained on oral levetiracetam 500 mg twice daily. The patient's symptoms quickly improved, and he was discharged the next day. Five weeks later, the diffusionweighted findings disappeared on a repeat brain MRI. *(continued next page)* *(Case Report continued from previous page)*

#### **Patient 4**

A 22-year-old woman with a history of left optic neuritis four years prior to admission came in with left face, arm, and leg numbness for three days. The numbness was patchy and not associated with any weakness or clumsiness.

On clinical examination, there was decreased light touch and temperature sensation on the left face, arm, and leg. There was no evidence of weakness, ataxia, or cranial nerve deficits. Vision was 20/20 in both eyes with intact color vision. Fundus examination showed no abnormalities in the optic nerve. There was no impairment of the extraocular movements. Her brain MRI (Fig. 2, Patient 4) showed a hyperintense cerebral lesion on DWI. The initial laboratory examination was normal including: erythrocyte sedimentation rate (ESR), lupus antibody, complete blood count, comprehensive metabolic panel, coagulation profile, serum vitamin B12 level, and rapid plasma reagin. Her cerebral spinal fluid (CSF) examination showed no evidence of infection, but revealed "eight" oligoclonal bands. A diagnosis of multiple sclerosis was made and the patient was started on disease modifying therapy.

#### **Patient 5**

A 59-year-old man with a history of hypertension and dyslipidemia came with right-sided weakness for eight hours prior to admission. He had a significant family history of cardiac disease. The initial clinical examination revealed normal mental status, speech, and cranial nerve examination. There was mild weakness of his right upper and lower extremities. His reflexes were symmetric, except for an extensor plantar response on the right. There was no ataxia. Laboratory exam showed normal complete blood count, comprehensive metabolic panel, electrocardiogram (EKG), cardiac enzymes, and coagulation profile. A CT scan of the brain was normal and the MRI of the brain (Fig. 2, Patient 5) showed left frontal lobe hyperintensity in diffusion-weighted imaging and corresponding hypointensity on ADC. T2 FLAIR images were hyperintense in the corresponding region.

### **Patient 6**

A 42-year-old man with a history of recent tooth extraction for a molar tooth abscess came to the hospital with a 2-day history of left-sided weakness. Relevant medication and medical history were unremarkable. On clinical examination he was febrile with a temperature of 101.4° F, but the rest of his vital signs were normal.

Neurologically, there was evidence of left upper motor neuron facial nerve palsy and mild left-sided weakness. MRI of the brain (Fig. 2, Patient 6) revealed a DWI hyperintense lesion in the right frontal lobe. An incisional biopsy of the lesion showed evidence of pus, which was drained and cultured. *Staphylococcus aureus* was isolated from the cultures. The patient did well after one month of intravenous vancomycin.

## **Discussion**

The most common cause of hyperintense lesions on DWI, commonly referred to as "positive" DWI, is ischemic stroke. MRI-DWI has been shown to be superior to conventional T2-WI in detecting acute ischemic stroke, whereas both techniques assist in determining the age of ischemia.<sup>4</sup>

In patients who present with symptoms of ischemic stroke, diffusion-weighted images are very helpful in identifying any area of acute ischemia and discriminating between new and old infarction, as well as other acute and chronic lesions in the brain. Only the acute infarcts appear hyperintense on the diffusion. Ischemic strokes on some occasions can be isointense on DWI. This is especially true when the MRI scan is obtained very early after the onset of symptoms or in some cases of small ischemic insults to the posterior circulation territory or other very small lacunar infarcts.<sup>5</sup> Just as a normal "negative" DWI does not always rule out the small possibility of ischemic stroke, a hyperintense (positive) lesion on DWI does not always mean ischemic stroke. The Table enlists the variety of disorders that have the potential to cause hyperintense signals on DWI.

Nonischemic lesions that appear very bright on T2-WI can cause hyperintense signals on DWI, also known as a T2-weighted shine through. This is the second most common cause of a hyperintense signal on DWI (after ischemic stroke). In these cases, ADC mapping plays a critical role in reaching the final diagnosis and only true restriction in diffusion, as seen in the case of ischemic stroke, gives a decreased signal on ADC. Therefore, in the overwhelming majority of cases, a low intensity signal on ADC mapping and a high intensity signal on DWI mostly signifies an ischemic infarct. $4,6$ 

Intracranial abscesses and metastasis $<sup>7</sup>$  may also exhibit</sup> restricted diffusion due to the presence of thick cellular necrotic debris, especially in the core of the lesion. The diagnosis in these cases is usually based on the signal differences observed on T1 and T2-weighted sequences and the presence or absence of contrast enhancements seen on T1-weighted images. For example, the MRI scan of patient 6 showed a low signal on ADC and a high signal on diffusion, a pattern similar to the one seen in ischemic stroke. However, there



**Fig. 1 Patient 1: Hyperintensity in the left frontoparietal region on diffusion-weighted imaging (DWI). Apparent diffusion coefficient map shows hyperintensity in the corresponding region. Corresponding regions on FLAIR imaging show hyperintensity with vasogenic edema in the surrounding areas. T1 with contrast sequence shows heterogenous contrast enhancement. Findings are suggestive of a primary malignant brain tumor, most likely malignant glioma. Patient 2: DWI shows hyperintensity in the left parietal region with corresponding hypointensity on ADC mapping. FLAIR imaging shows a rim of hyperintensity and subtle hypointensity in the center. T1 with contrast imaging shows hyperintensity with peripheral contrast enhancement. There is presence of peripheral hyperintensity in FLAIR images consistent with edema. These findings are consistent with late subacute hemorrhage. Patient 3: First diffusion DWI reveals a hyperintensity in the left temporal lobe. Repeat DWI after 5 weeks reveals the resolution of the hyperintensity. Corresponding FLAIR and ADC images were isointense on both instances. T1 with contrast images are unremarkable.** *DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; ADC, apparent diffusion coefficient.*

was evidence of vasogenic edema and contrast ring enhancement that are not typically seen in acute ischemic strokes, which is readily observed on T2 [FLAIR] and T1 after contrast images. Similarly, a late subacute bleed (Patient 2) can clinically and radiographically (hyperintense DWI) mimic an ischemic stroke. However, a hyperintense signal on T1-WI, which is seen with subacute intracranial hemorrhage, is not seen with ischemic stroke.<sup>8</sup> Additionally, other intracranial lesions, such as gliomas (Patient 1, Fig. 1) can show restricted

water diffusion that indicates high cellularity, which is highly indicative of a high-grade glioma.<sup>9</sup>

Current evidence suggests that DWI is also sensitive to detect demyelination in cases of multiple sclerosis. Multiple sclerosis plaques (which are primarily hyperintense on T2-weighted lesions) are caused by a breach of the normal tissue integrity and structure. This breach affects the diffusion of water molecules across the brain tissue resulting in a restricted diffusion signal. The ADC signal

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**Fig. 2 Patient 4: Hyperintense lesion on DWI and T2/FLAIR in right thalamus and internal capsule region. There is corresponding hypointensity with a rim of hyperintensity on apparent diffusion coefficient (ADC) maps. Additionally, there are T2 hyperintense lesions in the subcortical periventricular regions. T1 with contrast images are negative. Patient 5: DWI shows left frontal lobe hyperintensity and corresponding hypointensity on ADC. T2 FLAIR images show hyperintensity in the corresponding regions. These findings are consistent with an acute ischemic stroke. Patient 6. DWI shows hyperintense lesion in the right frontal lobe with corresponding hypointensity on ADC. There is evidence of edema as seen on ADC and FLAIR images which surround the lesion. Contrast enhancement shows ring enhancement.** *DWI, diffusion weighted imaging; FLAIR, fluid-attenuated inversion recovery; ADC, apparent diffusion coefficient*.

for multiple sclerosis lesions is usually hyperintense but can be isointense or hypointense. It has also been shown that a mean lesion ADC of secondary progressive multiple sclerosis was significantly higher than relapsing and remitting multiple sclerosis.<sup>10,11</sup>

Finally, an ictal, early postictal, or interictal state (Patient 3) can cause hyperintense lesions on DWI.<sup>12</sup> As previously described,<sup>12</sup> increased signal on DWI, with corresponding low or normal ADC, may be present in seizure patients. However, unlike stroke, the abnormalities in this case are reversible and do not follow a typical vascular distribution. The abnormalities are presumed to be due to transient cortical

irritability related to hypoperfusion in the epileptic zone<sup>13</sup> or transient vasogenic edema due to the breakdown of the bloodbrain barrier.<sup>14</sup>

## **Conclusion**

Our report emphasizes that despite DWI's high sensitivity in confirming ischemic stroke, not all hyperintense diffusion lesions are ischemic strokes. DWI's specificity for ischemic stroke is dependent on a given clinical scenario and interpretation of other imaging modalities of MRI (ADC, T2, T1, and FLAIR). Awareness and knowl-

#### **Table. Lesions that can be bright on diffusion-weighted imaging**

Acute and subacute ischemic infarct Venous infarcts Brain abscess Brain metastasis Acute demyelination (like multiple sclerosis plaques) Tumor undergoing central necrosis Tumor with high nuclear cytoplasmic ratio Acute encephalitis (as in herpes simplex encephalitis) Subacute hemorrhage Bright lesions on T2-weighted imaging (shine-through phenomenon) Seizure

edge of this imaging technique helps to enrich diagnostic skills and provides better insight to the correlation between clinical and radiological perspective of the disease, which eventually leads to the proper management.

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*Please see Dr. Mughis Sheerani's editorial on page 880 of this issue.*

*"Technology is a way of organizing the universe so that man doesn't have to experience it."*

—Max Frisch