Introduction

Diffusion-weighted magnetic resonance imaging (DWI) is a technique based on diffusion of water molecules in tissues with clinical applications to a wide array of pathological conditions. In vitro measurements of diffusion coefficients for liquids based on their nuclear magnetic resonance signal using the pulse field gradient method were originally described in the 1960s [1] and improved in the early 1970s [2]. These were followed by in vivo measurements of molecular diffusion of water and applications to various pathologic states in human and animal studies, including cerebral ischemia and neoplasms in the mid-1980s and early 1990s [3–14]. However, because of significant technical requirements of DWI, there has only been widespread clinical application of this technique in the last decade. Currently, DWI is the most reliable method for detection of early and small ischemic infarcts in the brain. However, applications of DWI extend far beyond the work-up of acute ischemia. DWI is increasingly used for the evaluation of a large variety of neoplastic and nonneoplastic conditions affecting the brain, head, and neck. This chapter begins with a description of the basic mechanisms underlying DWI changes on magnetic resonance imaging (MRI) scans, focusing on the extensive work using experimental models of brain ischemia. This is followed by a discussion of currently established and experimental clinical applications of DWI, starting with the use of DWI for imaging acute ischemic stroke. The physics of DWI is reviewed in a separate chapter and is not discussed here.

Basic Mechanisms Underlying Diffusion Changes in Pathologic States

Much of our understanding of the mechanisms underlying DWI changes in pathologic states is based on in vitro and in vivo experimental models of cerebral ischemia in animals. Cerebral ischemia results in diminished diffusion of water molecules within the infarct territory with a rapid decline in apparent diffusion coefficient (ADC) values. Based on current data, the decline in the ADC seen during acute ischemia can be attributed to a combination of complex biophysical factors resulting from disruption of normal cellular metabolism (Table 2.1). Disruption of normal cellular metabolism and depletion of adenosine triphosphate (ATP) stores result in failure of Na+/K+ ATPase and other ionic pumps with loss of ionic gradients across cellular membranes. This in turn leads to a net shift of water from the extracellular (EC) to the intracellular (IC) compartment with a change in the relative volume of these compartments as well as alterations in the IC and EC microenvironments. These alterations ultimately result in the restricted diffusion seen on MR imaging. Although there is some controversy regarding the biophysical determinants of diffusion changes seen on MRI, three major mechanisms are believed to account for the restricted diffusion seen during acute ischemia; they are (1) changes in relative volumes of the intracellular and extracellular spaces, (2) increased extracellular space tortuosity resulting in increased impedance to diffusion of water, and (3) diminished energy-dependent cytoplasmic circulation/microstreaming in the intracellular compartment. Some of the key investigations and controversies pertaining to mechanisms of DWI changes are summarized in the paragraphs that follow.

One widely proposed mechanism for the diffusion changes during cerebral ischemia is that disruption of energy metabolism results in failure of the Na+/K+ ATPase pump. This in turn leads to a net shift of water from the EC compartment, where the diffusion of water is relatively unimpeded, to the IC compartment where the diffusion of water is postulated to be...
relatively restricted [15]. This model is supported by animal studies demonstrating that ischemic infarction is associated with a reduction of the Na+/K+ ATPase pump activity [16], that pharmacologic inhibition of the Na+/K+ ATPase pump with ouabain in the absence of ischemia results in decreased ADC values [17, 18], and that nonischemic cytotoxic edema secondary to acute hyponatremia is associated with decreased ADC values [19]. However, the concept of relatively impeded diffusion of water in the IC compared to the EC compartment in not universally accepted, with some experiments supporting the theory [15] and others disputing it [20, 21].

Multiple investigations have demonstrated that alterations in the EC compartment can result in changes in diffusion seen on MRI [20–24]. Early DWI changes following transient ischemia in vivo correlate with shrinkage and reexpansion of the extracellular space [22]. In addition, based on observations on osmotically driven changes in compartment volume in ex vivo rat optic nerve preparations, it has been argued that assuming the IC and EC water constitute approximately 80% and 20% of total water in the brain, respectively, moderate fractional changes in cell volume can result in large changes in the contribution of the EC to the ADC [23]. Using these assumptions, it has been postulated that changes in the extracellular fraction are the main factor accounting for the ADC changes observed during ischemia [23]. Changes in relative compartment volume and associated cellular swelling may result in diffusion changes by increasing the tortuosity of the EC space, which in turn results in greater impedance to diffusion of water and the decreased ADC seen on MRI [20, 24].

Additional experiments suggest that changes in the intracellular microenvironment also contribute to the decreased ADC associated with acute ischemia. In experiments in which 2-[19F]fluoro-2-deoxyglucose-6-phosphate was used as a compartment-specific marker for the IC and EC compartments by manipulation of routes of administration, the ADC in both compartments were similar at baseline and both were similarly reduced following cerebral ischemia [20]. In addition, experiments using diffusion-weighted MR spectroscopy evaluating predominantly intracellular metabolites such as N-acetyl-aspartate and phosphocreatine (Cre) [25] or the potassium analog Cesium (Cs) [26] have also demonstrated a decrease in the ADC of the IC compartment following ischemia. In light of investigations suggesting that the diffusion in the IC and EC spaces may not be significantly different, it has been proposed that the changes in IC ADC are secondary to disruption of the energy-dependent cytoplasmic motion of molecules or microstreaming [20].

Increased cytoplasmic viscosity, such as from breakdown of intracellular organelles or cytoskeleton, is an alternate potential mechanism for changes in IC ADC. However, the increased IC water and cellular swelling in isolation would be expected to facilitate diffusion [27], and dissociation of the cytoskeleton likewise appears to facilitate diffusion of water in experimental models [27, 28], making this hypothesis less attractive. A number of other potential mechanisms of ADC change during acute ischemia have been discussed in the literature including changes in tissue temperature and membrane permeability. Although theoretically valid, they probably play a minor and insignificant role under typical circumstances in vivo during an acute stroke [20, 29].

### Table 2.1 Theories for decreased diffusion in acute stroke

<table>
<thead>
<tr>
<th>Theory</th>
<th>Description</th>
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<tbody>
<tr>
<td>Failure of Na+/K+ ATPase and other ionic pumps with loss of ionic gradients across membranes, net shift of water from the extracellular to the intracellular space, and changes in the relative volumes of intracellular and extracellular space</td>
<td></td>
</tr>
<tr>
<td>Decrease in the size of the extracellular space due to fluid shifts and cell swelling with a resultant increase in extracellular space tortuosity</td>
<td></td>
</tr>
<tr>
<td>Diminished energy-dependent intracellular cytoplasmic circulation/microstreaming</td>
<td></td>
</tr>
<tr>
<td>Increased intracellular viscosity and intracellular space tortuosity secondary to breakdown of organelles and the cytoskeleton</td>
<td></td>
</tr>
<tr>
<td>Increased cell membrane permeability</td>
<td></td>
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<tr>
<td>Temperature decrease</td>
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</tbody>
</table>

### Basic Principles of Diffusion-Weighted Imaging Map Interpretation

All DWI images (linearly T2 weighted and exponentially diffusion weighted) should be processed at the MR console with generation of ADC maps (linearly diffusion weighted, without a T2 component) and exponential images (exponentially diffusion weighted, without a T2 component) (Fig. 2.1). The use of the ADC map is essential for proper interpretation of DWI images since both areas of diminished and increased diffusion can appear bright on DWI images. In lesions with restricted diffusion such as acute ischemic strokes, the T2 and diffusion effects both cause increased signal on DWI, and the DWI images consequently have the highest contrast-to-noise ratio (Fig. 2.2). Areas of restricted diffusion also appear hyperintense on exponential images, although less bright, compared to the DWI image because of absence of the T2 effect (Fig. 2.2). Lesions with restricted diffusion appear dark on the ADC map (Fig. 2.2). Areas of increased diffusion, on the contrary, may appear hyperintense, isointense, or hypointense to normal brain parenchyma on DWI images depending on the strength of the T2 and diffusion components, but are hyperintense on the ADC map (Figs. 2.3 and 2.4). When a lesion is hyperintense on both the DWI image and the ADC map and hypointense on the exponential image, the phenomenon is referred to as T2 shine-through and may be seen with late subacute infarcts or chronic ischemic lesions (Fig. 2.4). Lesions with T2 shine-through may be misinterpreted as an acute infarct if findings on the ADC map or exponential image are not taken into account.
**Fig. 2.1** Normal diffusion MR maps. (a) Axial DWI, (b) ADC, and (c) exponential images demonstrate normal diffusion MR maps from a 24-year-old man \( b=1,000 \text{ s/mm}^2; \) TR, 5,000 ms; minimum echo time; matrix, 128×128; field of view, 22×22 cm; section thickness, 5 mm with 1 mm gap). DWI are linearly T2-weighted and exponentially diffusion-weighted, whereas exponential maps are linearly diffusion-weighted without a T2 component. Note how the normal cerebral cortex and deep gray nuclei have mildly increased intensity on DWI compared to adjacent white matter. Normal CSF spaces appear dark on DWI and exponential maps and bright on the ADC map given the lack of physical barriers to free motion of water. Abbreviations: SI Signal intensity, \( SI(T2W) \) Signal intensity on T2-weighted images.

**Fig. 2.2** Acute infarction. Diffusion MR maps from a 31-year-old man with embolic occlusion of the left M1 segment, imaged 3 h after developing aphasia and right hemiparesis, demonstrate a large area of signal abnormality in the left MCA territory that is (a) hyperintense on DWI, (b) hypointense on the ADC map, and (c) hyperintense on the exponential map consistent with restricted diffusion secondary to an acute infarction. (d) There is mild corresponding hyperintensity on the FLAIR image, although the infarct is more conspicuous on the DWI image

**Fig. 2.3** Chronic infarction on DWI. Axial MR images of a chronic left MCA territory infarction demonstrate (a) an area of heterogenous signal abnormality within the left MCA territory with local volume loss and associated ex-vacuo dilation of the left lateral ventricle on the FLAIR image. There is corresponding signal abnormality on the diffusion maps that is heterogenous, but (b) predominantly hypointense on DWI, (c) hyperintense on the ADC map, and (d) hypointense on the exponential image consistent with elevated diffusion.
Diffusion-Weighted Imaging of Ischemic Arterial Infarcts

Diffusion Characteristics of Ischemic Lesions at Different Stages

DWI is highly sensitive (81–100%) and specific (86–100%) for detection of acute ischemia within the first 12 h after stroke onset [30–34], with sensitivities and specificities approaching 100% at specialized high volume stroke centers (Tables 2.2 and 2.4, Figs. 2.2 and 2.5). DWI may demonstrate infarcts as early as 11 min after symptom onset [35] and is superior to conventional MRI or computed tomography (CT) in the first 3–6 h, at which time there is frequently insufficient accumulation of tissue water for reliable detection of hypointensity on CT and hyperintensity on T2 weighted and fluid-attenuated inversion recovery (FLAIR) MR images [30, 31, 34] (Fig. 2.5). In a recent prospective evaluation, MRI with DWI had a sensitivity of 73% and specificity of 92% for identification of ischemic infarcts within 3 h of symptom onset compared to a sensitivity of 12% and specificity of 100% for CT [30]. In another study, DWI had a sensitivity of 97% and specificity of 100% for identification of acute ischemia within 6 h of stroke symptom onset compared to 58% and 100%, respectively, for conventional MRI sequences and 40% and 92%, respectively, for CT [34]. Although most useful in the first 6–8 h when infarcts are frequently not identifiable on T2 or FLAIR images, DWI can also be valuable at later time points because of its higher contrast-to-noise ratio compared with CT and conventional MRI images. DWI has superior sensitivity for identification of small infarcts that may be overlooked on FLAIR or T2 images by increasing their conspicuity and enables distinction of small recent white matter infarcts from nonspecific T2 hyperintense white matter lesions [36, 37] (Fig. 2.6).

Following the onset of acute ischemia, there is a rapid decrease in water diffusion that is markedly hyperintense on DWI and hypointense on the ADC map and is generally postulated to represent cytotoxic edema (Table 2.2, Figs. 2.2, 2.5, and 2.7). After the initial period of decreased ADC values, there is a gradual increase in the ADC values secondary to cell lysis and increasing vasogenic edema, with a transient return to baseline known as pseudonormalization, a period during which the ADC of the nonviable ischemic tissue is similar to normal brain ADC (Fig. 2.7). In animal models of stroke, ADC values are reduced for a very short period of time and return to baseline between approximately 24–48 h [38, 39]. In humans, the peak signal reduction on ADC occurs between 1 and 4 days, with a return to baseline at approximately 4–10 days following the ictus [40–44]. The DWI at this stage is typically hyperintense to normal brain parenchyma. Subsequently, as the infarct progresses to a more chronic stage, there is a progressive increase in the ADC of an ischemic lesion. This is secondary to increased water content as well as emerging gliosis and cavitation, which result in breakdown of the normal tissue structure and barriers to free diffusion of water molecules. During the chronic stage, an infarct can be mildly hyperintense, isointense, or hypointense to normal brain parenchyma on DWI and hypointense on ADC depending on the strength of the T2 effects and diffusion, but should be hyperintense on ADC and hypointense on exponential images (Figs. 2.3 and 2.7).

Although separation of infarct stages into hyperacute, acute, subacute, and chronic (Table 2.2) provides a useful general framework for dating an infarct on MRI, there is variability in the time course of the DWI and ADC signal changes of evolving infarcts. A number of factors including infarct type, patient age, and reperfusion status affect the evolution of signal changes observed on MRI. In one study,
<table>
<thead>
<tr>
<th>Pulse sequence</th>
<th>Hyperacute (0–6 h)</th>
<th>Acute (6–24 h)</th>
<th>Early subacute (2–7 days)</th>
<th>Late subacute (8–21 days)</th>
<th>Chronic weeks – months</th>
</tr>
</thead>
<tbody>
<tr>
<td>DWI</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Hyperintense Gyral hypointensity from petechial hemorrhage</td>
<td>Hyperintense (secondary to T2 component)</td>
<td>Isointense to hypointense</td>
</tr>
<tr>
<td>ADC</td>
<td>Hypointense</td>
<td>Hypointense</td>
<td>Hypointense to isointense&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hypointense to hypointense&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Exponential</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Hyperintense to isointense&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Hyperintense to hypointense&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Hypointense</td>
</tr>
<tr>
<td>Histopathologic changes</td>
<td>Cytotoxic edema</td>
<td>Cytotoxic edema</td>
<td>Cytotoxic edema with a small amount of vasogenic edema</td>
<td>Cytotoxic and vasogenic edema</td>
<td>Resolving vasogenic edema followed by gliosis and tissue loss</td>
</tr>
</tbody>
</table>

<sup>a</sup>The provided timelines are approximate and can vary between patients and depending on infarct type

<sup>b</sup>Pseudonormalization, a period during which the ADC of nonviable ischemic tissue is similar to normal brain ADC, most commonly occurs between 4 and 10 days post ictus in humans, and can overlap the early and late subacute stages

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**Fig. 2.5** Superiority of DWI imaging for detection of early ischemic change compared to FLAIR images. (a) Axial DWI and (b) ADC images from an 89-year-old man with a history of acute aphasia and right hemiparesis of 4-h duration demonstrate a large area of restricted diffusion, (c) without any significant corresponding signal abnormality on the FLAIR image

**Fig. 2.6** Distinction of acute white matter infarctions from chronic white matter change based on diffusion characteristics. (a) There is a focus of hypoattenuation in the left corona radiata on computed tomography (CT) with (b) corresponding hyperintensity on the FLAIR image that is age indeterminate and indistinguishable from the remainder of white matter abnormalities. However, (c) the DWI and (d) ADC images clearly distinguish this acute infarct from nonspecific white matter changes by demonstrating restricted diffusion in the acute infarction and elevated diffusion in the nonspecific white matter changes
Fig. 2.7 Temporal evolution of infarction on diffusion maps. 
(a–e) Axial DWI images and (f–j) ADC maps demonstrate the appearance of different infarct stages on diffusion maps. At 6 h, the right middle cerebral artery (MCA) territory infarction is mildly hyperintense on DWI images and hypointense on ADC maps secondary to early cytotoxic edema. By 30 h, the DWI hyperintensity and ADC hypointensity are pronounced secondary to increased cytotoxic edema. This is the ADC nadir. By 5 days, the ADC hypointensity is mild and the ADC has nearly pseudonormalized due to cell lysis and the development of vasogenic edema. The lesion remains hyperintense on the DWI images because the T2 and diffusion components are combined. At 3 months, the infarction is hypointense on DWI and hyperintense on ADC maps due to increased diffusion secondary to the development of gliosis and tissue cavitation.
the transition from decreasing to increasing ADC values occurred earlier in nonlacunar infarcts than lacunar infarcts [45]. The same study also found a trend toward earlier transition to increasing ADCs of nonlacunar infarcts in patients older than a median age of 66 [45]. In another study, there was slightly faster recovery (increase) in ADC values of infarcted gray matter compared to white matter [43]. Early reperfusion, as seen after treatment with thrombolytic therapy, also changes the evolution of diffusion abnormalities and is discussed later in the section on DWI reversibility.

Reliability and Pitfalls of Diffusion-Weighted Imaging in Identification of Acute Ischemic Lesions

Despite its exquisite sensitivity for detection of acute ischemic lesions, DWI is not infallible. Although false-negative DWI results have been described in many cerebral arterial territories and for different lesion sizes, small punctate infarcts and infarcts located within the brainstem, especially those imaged at less than 12 h from symptom onset, have the highest likelihood of a false-negative DWI study [36, 46–53]. Among brainstem infarcts, medullary infarcts appear to be the most difficult to detect. Proximity to skull base structures resulting in susceptibility artifact and differences in anatomic composition and organization of the normal fiber tracts in this region are likely contributing factors [46].

In cases of clinically suspected strokes, where no infarct is identified on the initial axial DWI scan, obtaining images with a higher resolution and/or in the coronal plane may reveal an infarct (Fig. 2.8). Another approach for increasing sensitivity is acquisition of DWI at a b-value of 2,000 s/mm² or higher. Some studies have demonstrated mildly increased sensitivity and increased conspicuity of ischemic lesions at higher b-values, but this comes at the expense of decreased signal-to-noise ratio and increased imaging time and a clear diagnostic benefit remains to be proven [54–57]. In addition, in one study of patients with transient ischemic attacks (TIA), the use of thinner DWI sections increased the sensitivity for detection of small ischemic lesions [58]. However, the increased acquisition time and associated propensity for motion degradation in this patient population may preclude widespread application of this technique in the evaluation of acute stroke. In any case, a short-term follow-up MRI scan within 24 h should identify most small infarcts not visible on the initial study. A team approach is essential since correlation with clinical signs and symptoms may bring into attention regions of potential abnormality that would otherwise be dismissed as artifact.

Recently, 3 Tesla (T) magnets have been used to evaluate acute ischemic stroke. In a prospective study comparing 1.5 and 3T acquisitions in 25 patients with clinical symptoms of acute (7/25) or subacute ischemia (18/25), there was increased contrast-to-noise ratio on 3T and a greater number of small ischemic lesions were identified on 3T compared to 1.5T, although all patients with infarcts on 3T had at least one identifiable infarct on their 1.5T images [59]. Six of 25 patients had no DWI abnormality on either 3T or 1.5T images and were diagnosed with a TIA. There was increased image distortion at 3T compared to 1.5T, although this may be overcome in the future with advances in image acquisition.

False-positive DWI findings may occur secondary to T2 shine-through, as discussed earlier, and can be readily distinguished from true restricted diffusion if the DWI images are interpreted in conjunction with the ADC or exponential maps. In addition, a variety of nonischemic lesions may have diminished diffusion and could potentially be mistaken for infarcts (Table 2.3), as discussed in the following sections. Most are readily distinguishable from acute infarcts when the DWI findings are considered in conjunction

Fig. 2.8 Acute pontine infarct. Axial DWI images demonstrate mild hyperintensity in the ventral left pontine tegmentum that could represent (a) artifact, but (b) has an appearance suggestive of a true focus of restricted diffusion on one image. (c, d) Coronal DWI images unequivocally demonstrate restricted diffusion from a small perforator infarction.
with findings on conventional MR sequences such as T2, FLAIR, and pre- and post gadolinium T1-weighted images. However, hypoglycemia and acute demyelinating disease can present with acute neurologic deficits and a single non-enhancing FLAIR hyperintense lesion with restricted diffusion, and are at times misdiagnosed as acute strokes.

**Table 2.3** Nonischemic lesions that may have restricted diffusion on DWI

<table>
<thead>
<tr>
<th>Entity</th>
<th>Proposed cause of restricted diffusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral abscess</td>
<td>Increased viscosity</td>
</tr>
<tr>
<td>Neoplasms such as lymphoma and high-grade</td>
<td>Dense cell packing</td>
</tr>
<tr>
<td>Venous infarcts</td>
<td>Cytotoxic edema</td>
</tr>
<tr>
<td>Acute demyelinating lesions</td>
<td>Cytotoxic edema and/or inflammatory</td>
</tr>
<tr>
<td>Acneumal edema</td>
<td>cell infiltrates? myelin vacuolization</td>
</tr>
<tr>
<td>Encephalitides – Herpes simplex virus</td>
<td>Cytotoxic edema</td>
</tr>
<tr>
<td>Hemorrhage – oxyhemoglobin, extracellular</td>
<td>? Intracellular for oxyhemoglobin and</td>
</tr>
<tr>
<td>methemoglobin</td>
<td>? increased viscosity for both</td>
</tr>
<tr>
<td>Diffuse axonal injury</td>
<td>Cytotoxic edema, axonal retraction balls</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Cytotoxic edema</td>
</tr>
<tr>
<td>Hemiplegic migraine</td>
<td>Cytotoxic edema, ? spreading depression</td>
</tr>
<tr>
<td>Seizures</td>
<td>Cytotoxic edema</td>
</tr>
<tr>
<td>Transient global amnesia</td>
<td>Cytotoxic edema, ? spreading depression</td>
</tr>
<tr>
<td>Heroin-induced leukoencephalopathy</td>
<td>? Myelin vacuolization</td>
</tr>
<tr>
<td>Metronidazole toxicity</td>
<td>? Cytotoxic edema</td>
</tr>
<tr>
<td>Cretzfeldt Jakob disease</td>
<td>Spongiform change</td>
</tr>
<tr>
<td>Osmotic myelinolysis</td>
<td>? Cytotoxic edema, ? myelin vacuolization</td>
</tr>
<tr>
<td>Carbon monoxide poisoning</td>
<td>Cytotoxic edema</td>
</tr>
</tbody>
</table>

**Table 2.4** DWI use for imaging of acute stroke: Key concepts

- DWI is the gold standard for identifying infarct core in acute ischemic stroke
- DWI has sensitivity and specificity over 95% in high volume stroke centers with experienced neuroradiologists. Scanning with higher resolution DWI sequences, a b-value of 2,000 s/mm² or higher, and/or on a 3T scanner may increase sensitivity
- The rare acute infarcts not detected on DWI are usually punctate infarcts in the brainstem or deep gray nuclei
- Single lesions with restricted diffusion confused with acute stroke are frequently due to hypoglycemia or demyelinating disease
- DWI reversibility (abnormal on initial DWI but normal on follow-up T2 or FLAIR at 1 week or later) is rare. Greater reversibility of DWI positive lesions has been demonstrated after recanalization following intravenous or intra-arterial thrombolysis. DWI reversibility is overestimated in some studies due to tissue loss at follow-up imaging at 30–90 days. Threshold ADC values for DWI reversibility have not reliably been established
- DWI lesion volume correlates with clinical outcome scales and is an independent predictor of outcome in multiple studies. The correlation depends on lesion location. DWI lesion volume greater than one-third of the expected MCA territory or 100 mL is associated with poor outcome regardless of reperfusion therapy. It is used by some as an exclusion criterion for thrombolytic therapy
- DWI lesion greater than 100 mL is associated with an increased risk of hemorrhagic transformation. Mean ADC of less than 300×10⁻⁶mm²/s in the DWI positive lesion is predictive of symptomatic HT

**Reversibility of DWI Positive Lesions in Ischemic Stroke and the Use of DWI for Determination of Infarct Core**

It is generally accepted that diffusion-weighted imaging is the best method for identifying infarct core or tissue that will progress to infarction (Table 2.4). In the absence of early reperfusion in the setting of intravenous thrombolytic therapy or intra-arterial recanalization procedures, reversibility of restricted diffusion (defined as DWI abnormality on the initial scan without any corresponding abnormality on follow-up FLAIR or T2-weighted MRI scans) is very rare. In fact, frequently, the final infarct volume not only includes the initial area of diffusion abnormality but also extends to involve surrounding tissues [60–62].

Significantly higher rates of partial diffusion reversal have been reported after early reperfusion secondary to thrombolytic therapy [63–65] (Fig. 2.9). In one retrospective study of patients treated with intra-arterial thrombolysis, 19% had some reversal of DWI hyperintense regions on follow-up imaging [65]. In another study, 18 patients treated with intra-arterial or combined intravenous and intra-arterial thrombolytic therapy resulting in recanalization were evaluated with MRI before treatment, early after treatment, and on day 7 post-treatment [64]. The authors reported partial or complete normalization of diffusion abnormalities in 8/18 (44%) of patients on the early posttreatment scan, although in 5/8 patients (63%) there was partial or complete reappearance of the lesion on the MRI performed on day 7. The authors referred to this as late secondary injury, although the transient reversal may have represented a pseudonormalization-like phenomenon in which the MRI findings transiently resolved despite tissue injury, similar to observations in animal experiments in which transient reversal of MRI findings may be seen despite histopathologic evidence of tissue injury [66]. Persistent normalization of all reversed tissue was seen in 3/8 (38%, or 17% of all patients) on the scan performed on day 7. A voxel-by-voxel analysis of the regions of DWI abnormality
in all patients combined was also performed and demonstrated a sustained reversal of 33% in addition to a late reversal of 8% (i.e., persistent diffusion abnormality on the early posttreatment scan but normal DWI/T2W characteristics on the day 7 scan). In a more recent analysis of 32 patients from a prospective multicenter trial of treatment with IV thrombolysis within 3–6 h of stroke onset (DEFUSE trial: Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution), the authors reported a median reversal rate of 43% by comparing final infarct volumes on FLAIR images obtained at 30 days post-ictus with the total baseline DWI lesion volume.

The DWI reversal rate was greater in regions with normal baseline perfusion, in patients with early recanalization, and among cases with a favorable clinical outcome. While there is evidence to support some degree of DWI reversibility after early reperfusion, the determination of the percentage of DWI reversibility is not straightforward. In animal studies, exposure to short periods of ischemia can result in a transient decline in ADC with normalization after cessation of the ischemic insult. However, despite complete normalization on imaging, there can be selective neuronal injury on histopathology that is below the threshold of the imaging technique. Another technical factor that may result in an overestimation of DWI reversibility on follow-up imaging is volume loss and tissue retraction during the chronic stage that may result in an underestimation of final infarct volume.

In general, tissues with a higher absolute ADC value tend to have a higher likelihood of reversibility. Based on this premise, some have tried to determine an ADC threshold for tissue infarction. However, there is significant variation in the reported ADC values of irreversibly damaged ischemic tissue and of DWI reversible tissue and there is much overlap between the two. Furthermore, it has been demonstrated that even tissues with severely diminished ADC may recover. Apart from the ADC value, the duration and severity of ischemia and tissue perfusion status have been shown to represent important determinants of final infarct volume in animal and human studies. Therefore, although tissues with severely reduced ADC have a higher likelihood of progressing to an irreversible infarct, it is likely that ADC values alone are insufficient for absolute determination of tissue viability.

Use of DWI for Predicting Hemorrhagic Transformation of Ischemic Infarcts

Hemorrhagic transformation (HT) of brain infarcts represents secondary bleeding into ischemic tissue that occurs after the initial ictus. The reported incidence of HT across different studies varies widely because of differences in the definitions, modalities, and time frames used to evaluate for hemorrhage. However, the incidence of HT is clearly

![Fig. 2.9 DWI reversibility. A 69-year-old man presenting with acute dysarthria and right-sided weakness who was treated with intra-arterial thrombolysis with successful recanalization of a left M1 clot 6 h after symptom onset. (a–c) DWI and (d–f) ADC images obtained prior to therapy demonstrate restricted diffusion consistent with acute ischemia involving the left insula, basal ganglia, corona radiata, and frontal subcortical white matter. (g, h) On follow-up T2-weighted images there is T2 hyperintensity, consistent with infarction, in the left insula, basal ganglia, and frontal subcortical white matter. However, the residual corona radiata infarction appears smaller than on the initial diffusion maps.](image)
increased after thrombolytic therapy and ranges from 6% up to 44% if susceptibility-sensitive MR sequences such as gradient echo sequence are used, although the incidence of symptomatic HT is significantly lower \[75–83\].

Given that ADC values are believed to represent the severity and extent of ischemia, a number of investigators have assessed the value of ADC in predicting HT. In a retrospective analysis of 27 patients with acute stroke who underwent DWI and perfusion-weighted MRI, the investigators demonstrated that the mean ADC of ischemic regions that underwent HT \(510 \pm 140 \times 10^{-6} \text{ mm}^2/\text{s}\) was significantly lower than the overall mean ADC of all ischemic areas analyzed \(623 \pm 113 \times 10^{-6} \text{ mm}^2/\text{s}\) \[84\] (Fig. 2.10). The authors also noted that a persistent perfusion deficit within the infarct bed on the MRI performed 3–6 hours after the baseline scan was associated with a higher risk of HT within that area. Another investigation of 29 patients treated with intravenous thrombolytic therapy demonstrated that the absolute number (or volume) of voxels with ADC \(\leq 550 \times 10^{-6} \text{ mm}^2/\text{s}\) correlated with HT \[85\]. In a third study, using a monovariate model, the authors concluded that a mean ADC of less than \(300 \times 10^{-6} \text{ mm}^2/\text{s}\) in the infarct core was predictive of symptomatic HT \[86\]. However, despite these studies, other investigations have not found a statistically significant difference in the ADC of infarcts that subsequently underwent HT \[83\]. Thus, the clinical utility of ADC values in determining HT and its use for exclusion of patients from thrombolytic therapy remains unproven and requires further investigation.

The utility of initial DWI volume has also been evaluated as a potential predictor of HT. In a study of 645 patients with anterior circulation strokes treated with intravenous or intra-arterial thrombolysis, increasing DWI lesion size was associated with an increase in symptomatic HT. DWI lesion size was also found to be an independent risk factor when including National Institutes of Health Stroke Scale (NIHSS), age, time to thrombolysis, and leukoariosis using logistic regression analysis \[87\]. The highest risk for symptomatic HT was 16.1% and was observed in the subgroup with a large DWI abnormality, defined as \(>100 \text{ mL}\).

More recent work suggests that MR cerebral blood volume values may predict hemorrhagic transformation of acute ischemic stroke better than ADC values or initial DWI volume. In an analysis of 91 patients from the Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET), very
low cerebral blood volume (VLCBV2.5) (defined as MR cerebral blood volume at or below the 2.5th percentile) was found to predict all (i.e., not just symptomatic) HT better than DWI lesion volume and thresholded (<550 × 10−6 mm²/s) ADC lesion volume both in receiver operating characteristic analysis and logistic regression, although all three parameters were found to be significant in univariate analysis [88]. In another study of 184 patients, a large area with a severe perfusion deficit, defined as a $T_{max}$ of >8s, along with aggressive therapy (defined as endovascular treatment with or without intravenous tissue plasminogen activator administration) were found to correlate with radiological HT whereas DWI volume did not [89]. A number of other imaging parameters are associated with an increased risk of hemorrhagic transformation and include increased permeability on dynamic contrast-enhanced T1 MRI [90] and early parenchymal enhancement [91]. A detailed discussion of these techniques is beyond the scope this chapter.

Extrapolating from studies using CT scans in which hypotenuation involving greater than one-third of the middle cerebral artery (MCA) territory was associated with an increased risk of hemorrhagic transformation and poor outcomes following the administration of IV tissue plasminogen activator (tPA) [92], some clinicians consider a DWI lesion volume greater than one-third of the expected MCA territory a contraindication to the use of IV thrombolytic therapy and/or intra-arterial recanalization procedures. However, there remains lack of a widely accepted consensus on the use of DWI and other MR parameters for determination of risk of HT (Table 2.4).

Correlation of DWI Lesion Volume with Clinical Outcome

Initial DWI and ADC lesion volumes correlate with clinical outcome measured by various acute and chronic neurologic assessment tests including the NIHSS, the Glasgow Outcome Scale, the Barthel Index, and the Rankin or Modified Rankin Scale [42, 61, 62, 93–96]. Reported correlations range from $r$=0.56 to 0.73 and in some studies are stronger for cortical strokes than for penetrator artery strokes [42]. The variation in correlation of lesion size with the clinical score is not surprising. Given that many of the commonly used clinical scoring systems are weighted toward motor symptoms and the left hemisphere, lesion location [42, 93] can result in a significant discrepancy between total burden of disease and clinical score. For example, a small brainstem lesion affecting a compact motor fiber tract may result in high clinical scores, whereas a similarly sized lesion in the frontal lobe may not have a detectable associated abnormality on standard clinical scoring systems. This would also explain why some studies have failed to find a correlation between DWI volume and clinical outcome in infratentorial strokes [36].

Regardless of these variations, there is emerging evidence that patients with a DWI lesion volume of greater than approximately 70 mL do poorly regardless of treatment and recanalization status [97–100]. For example, Yoo et al. [99] demonstrated that in 54 patients treated mainly with IV TPA or heparin, all patients with a DWI lesion volume of greater than 72 mL had a poor outcome (modified Rankin Score = 3–6). Furthermore, in a retrospective analysis of 34 patients with anterior circulation strokes who underwent intra-arterial reperfusion therapy with or without IV thrombolysis, the same authors found that all patients (6/34) with an initial DWI lesion volume of >70 cm³ had poor outcome, in spite of a 50% recanalization rate [100]. In another study analyzing 98 patients from the EPITHET trial, Parsons et al. [98] found that while patients with an initial DWI lesion volume of 18 mL had substantially improved chances of a good outcome if treated with IV tPA, the odds of a benefit dropped rapidly at larger volumes and there was little treatment benefit with a DWI lesion volume >25 mL. Similar to the observations by Yoo et al., the authors from this study found that a large initial DWI lesion volume of >65 mL was strongly associated with a poor outcome.

Transient Ischemic Attacks

TIAs have been classically defined as any sudden focal neurologic deficit of presumed vascular origin with symptoms lasting less than 24 h [101, 102]. The classic definition of a TIA is based on studies from the 1950s and 1960s, at which time noninvasive diagnostic techniques were not available to evaluate for tissue injury [102]. This definition has been demonstrated to be outdated and unreliable, given that a substantial percentage of clinically defined TIAs have evidence of tissue injury on DWI consistent with small infarcts [101–105]. Furthermore, in addition to being outdated, the classic definition of a TIA can be potentially misleading, giving a false impression of a benign process rather than a potentially serious and urgent condition that requires prompt investigation. It has been shown that 21–48% of patients presenting with a “classic” TIA have DWI hyperintense lesions consistent with infarcts. These patients are at a higher risk for future vascular events (compared to those with “classic” TIA who do not have DWI hyperintense lesions) [103–107]. In one study, 19.4% of patients presenting with transient neurologic symptoms and evidence of infarction on DWI had in-hospital recurrent ischemic stroke and TIAs compared to 1.3% of patients with ischemic stroke (i.e., not a clinical TIA/transient neurologic symptoms) [108].
Venous Infarctions and Other Vascular Vasogenic Edema Syndromes

Vasogenic edema syndromes presenting with acute neurologic deficits can mimic acute ischemic stroke clinically. Furthermore, conventional MR sequences such as T2 and FLAIR cannot distinguish cytotoxic from vasogenic edema because both produce hyperintensity and can involve gray and/or white matter. However, DWI can be used to differentiate the two types of edema. Depending on the contributions from T2 effects, vasogenic edema may appear hypointense, isointense, or hyperintense on DWI. However, while cytotoxic edema is hypointense on the ADC map, vasogenic edema is hyperintense.

Venous Infarctions

Cerebral venous thrombosis (CVT) is an often underdiagnosed condition with a nonspecific clinical presentation and a large variety of underlying etiologic factors. The diagnosis of CVT requires a high index of clinical suspicion and a combination of conventional MRI and vascular imaging. Both nonhemorrhagic and hemorrhagic intraparenchymal lesions can be seen on conventional MRI. Nonhemorrhagic lesions consist of areas of T2 prolongation that typically do not conform to the major arterial territories [109]. These regions may have elevated diffusion, restricted diffusion, or both [109–112] (Fig. 2.11, Table 2.6) [111, 112]. The foci of elevated diffusion representing vasogenic edema are thought to result from increased vascular pressure and leaky vessels and usually resolve on follow-up [109, 110]. Foci of restricted diffusion representing cytotoxic edema may progress to permanent tissue damage or be reversible. In one study, reversible areas of restricted diffusion were seen only in patients with seizures [109]. Hemorrhagic lesions can have a variable appearance on DWI. Both oxyhemoglobin (seen in the first few hours) and extracellular methemoglobin (seen at a few weeks to a few months) are characterized by decreased diffusion (Fig. 2.12). Other products of hemorrhage (deoxyhemoglobin, intracellular methemoglobin, and hemosiderin) have decreased signal due to susceptibility effects on DWI, and a diffusion coefficient cannot be calculated.

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) can occur in association with a wide variety of clinical entities including acute hypertension, various hematologic disorders, treatment with immunosuppressive agents, and treatment with chemotherapeutic agents. The pathophysiology of PRES is controversial but believed to be secondary to endothelial dysfunction and failure of cerebral autoregulation with capillary leakage. On MRI, PRES is characterized by relatively symmetric patchy or confluent areas of bilateral T2 prolongation involving the subcortical white matter and overlying cortex. There is frequent involvement of the parieto-occipital areas, posterior temporal lobes, and posterior fossa structures such as the cerebellum and brainstem [113–116] (Fig. 2.13, Table 2.6). However, anterior circulation lesions are not uncommon and are frequently located in a border zone distribution between the anterior, middle, and posterior cerebral arteries [114–118]. Rare variants of PRES with a unilateral distribution or involving only the medulla oblongata have also been described [114, 119]. Most frequently, areas of T2 prolongation in PRES are secondary to vasogenic edema and appear slightly hypointense, isointense, or mildly hyperintense on DWI images with increased signal on the ADC map [113–117, 120] (Fig. 2.13). This is helpful since posterior distribution lesions can mimic basilar tip occlusion with arterial infarctions and border zone lesions can mimic watershed infarctions both clinically and on T2-weighted sequences. However, acute arterial and watershed infarctions can be distinguished using DWI since they have restricted diffusion. The clinical deficits and MR abnormalities in PRES are typically reversible [114, 118]. Occasionally, some
lesions may display transiently restricted diffusion and rarely small areas of restricted diffusion or tissue initially characterized by elevated or normal diffusion may progress to infarction [114, 115, 118]. One study reports greater reversibility of cortical and subcortical lesions compared to deep white matter or brainstem lesions [120].

### Hyperperfusion Syndrome Following Carotid Endarterectomy

Hyperperfusion syndrome (HS) is a relatively uncommon complication of carotid endarterectomy that is believed to occur as a result of post-revascularization changes in cerebral hemodynamics and impairment of cerebral autoregulation. It is thought that similar to PRES, increased pressure damages endothelial tight junctions, leading to a capillary leak syndrome. Patients with HS typically present with a unilateral headache, face and eye pain, and seizures, but may also have focal neurologic deficits [121]. In addition to areas of parenchymal hemorrhage, T2 and FLAIR images demonstrate hyperintense areas within the ipsilateral anterior circulation territory that can mimic arterial infarction but typically have elevated diffusion consistent with vasogenic edema [122–125] (Fig. 2.14, Table 2.6). Small embolic infarcts presenting as tiny foci of restricted diffusion can occur after CEA [124, 125] and should not be confused with or attributed to HS. Some studies describe transient cytotoxic edema in HS based on hyperintensity on DWI images, although the findings on the ADC map are not always clearly described making it difficult to exclude T2 shine-through with certainty.

**Table 2.6** MR findings of venous sinus thrombosis and other vascular vasogenic edema syndromes that can mimic acute stroke

<table>
<thead>
<tr>
<th>Venous sinus thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic and nonhemorrhagic lesions typically not corresponding to major arterial territories</td>
</tr>
<tr>
<td>Nonhemorrhagic lesions present as areas of T2 prolongation. These lesions may have elevated diffusion, restricted diffusion, or both. Lesions with elevated diffusion likely represent vasogenic edema and resolve. Lesions with decreased diffusion likely represent cytotoxic edema and may resolve (especially if associated with seizures) or progress to permanent injury</td>
</tr>
<tr>
<td>Posterior reversible encephalopathy syndrome (PRES)</td>
</tr>
<tr>
<td>Conventional MR findings include patchy bilateral areas of cortical and subcortical T2 prolongation in a predominantly posterior distribution and/or the border zones between the ACAs, MCAs, and PCAs. Both patterns can mimic acute stroke</td>
</tr>
<tr>
<td>Unlike acute stroke, lesions typically represent vasogenic edema, are usually isointense or mildly hyperintense on DWI, have elevated ADC values, and usually resolve</td>
</tr>
<tr>
<td>Occasionally, lesions may have transiently restricted diffusion or progress to infarction</td>
</tr>
<tr>
<td>Hyperperfusion syndrome (HS) post carotid endarterectomy</td>
</tr>
<tr>
<td>Typical MR findings consist of areas of T2 prolongation within the ipsilateral anterior circulation territory that mimic acute ischemia</td>
</tr>
<tr>
<td>Lesions are isointense to mildly hyperintense on DWI but have elevated ADC consistent with vasogenic edema, and resolve</td>
</tr>
</tbody>
</table>

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Fig. 2.11 Transient diffusion changes in cerebral venous sinus thrombosis. (a) A 3-D reformatted image from a CT venogram demonstrates no opacification of the anterior two-thirds of the superior sagittal sinus (SSS) consistent with thrombosis. (b) There is bilateral cortical and subcortical FLAIR hyperintensity, consistent with edema. (c) Some areas are hyperintense on DWI and (d) hypointense on ADC (short arrow) consistent with diminished diffusion due to cytotoxic edema. (d) Other areas are hyperintense on ADC (long arrow), consistent with vasogenic edema. The patient was successfully anticoagulated with partial recanalization of the SSS and no detectable residual parenchymal abnormality on (e, f) follow-up FLAIR images performed 1 month later.
Since patients with HS can present with seizures, this represents an additional potential etiology of transiently restricted diffusion on MRI.

**Transient Global Amnesia**

Transient global amnesia (TGA) is characterized by sudden onset of profound memory impairment resulting in both retrograde and antegrade amnesia [128] (Table 2.7). The amnestic syndrome typically resolves spontaneously within 24 h, although some impairment of cognitive function may persist beyond that time period [128, 129]. The etiology of TGA is controversial; some articles propose ischemia as an etiologic factor, while others propose spreading depression, among other theories. Regardless of the mechanism, punctate DWI hyperintense foci have been reported in 41–100% of TGA cases imaged within the first 3 days after the event, depending on the time lag for imaging and use of specialized sequences (described later). These lesions typically measure 1–3 mm in diameter and involve the lateral aspect of the hippocampus [129–133] (Fig. 2.15). Lesions are most frequently unilateral, but may involve the hippocampal formations bilaterally or present as multiple (2 to 3) lesions on the same side [130, 132–136]. In a small percentage of cases, lesions have also been reported in the splenium of the corpus callosum, cerebellum, or temporal lobe not involving the hippocampus [130, 133, 136, 137]. Frequently, no corresponding abnormality is detectable on follow-up MRI (either because of complete resolution or because the residual lesion is below the threshold of detection on T2 or FLAIR images), although occasionally the initial DWI abnormality may evolve into a T2/FLAIR hyperintense lesion consistent with a small infarct [130, 135].

Multiple studies have demonstrated that the timeline of imaging after symptom onset has a significant impact on lesion detection. In one study performing serial MRIs for 3 days, only 2/31 (6%) had detectable lesions when imaged within 2–8 h, but 23/31 (74%) and 26/31 (84%) had a DWI hyperintense lesion if imaged after 24 h or after 48 h from symptom onset, respectively [129]. At least two other studies demonstrate increased sensitivity when imaging is performed within 12–72 h [130] or at 3 days [133], compared to imaging within the first 12 h or first 24 h, respectively. However, one study reported a 100% sensitivity (20/20 patients) when patients were imaged in the first 24 h, although this study employed specialized DWI sequences including thinner section and coronal acquisitions that may explain the increased sensitivity for lesion detection [132]. In general, sensitivity for lesion detection is greatest 24–72 h after symptom onset [129, 130, 133]. The use of thinner sections (3 mm compared to 5 mm), a higher b-value (2,000 or 3,000 s/mm²), or a 3T scanner may also increase sensitivity for lesion detection [132, 133, 138].

**Hemiplegic Migraine**

Hemiplegic migraine is a rare subtype of migraine characterized by some degree of transient hemiparesis in addition to visual, somatosensory, or dysphasic symptoms, although some patients may have progressive cerebellar dysfunction as well. Usually, no abnormality is detected on MRI, but occasionally patients with prolonged hemiplegic migraine may have FLAIR and DWI hyperintensity involving the cortex and subcortical white matter, with or without corresponding hypointensity on the ADC map [139–145], which can be confused with an acute infarct (Fig. 2.16). A number of factors
can distinguish these lesions from acute stroke: (1) the patients usually have a strong history of migraines; (2) the lesions may cover multiple arterial territories [145]; (3) perfusion is usually normal or elevated [142–144, 146]; (4) angiography may demonstrate transient vessel dilation [146], be normal, or show vasospasm [147], but vessel cut-offs are not identified; and (5) the lesions and clinical deficits are usually reversible (Table 2.8). Other abnormalities that may be seen on MRI in patients with hemiplegic migraine include cerebral atrophy contralateral to the side with restricted diffusion in patients with hemiparetic auras of alternating sides [139] or cerebellar atrophy with increased ADC values [148].
Seizures can result in transiently decreased diffusion in animals and humans, likely secondary to transient cytotoxic edema [149–156] (Figs. 2.17 and 2.18, Table 2.9). A number of factors can help distinguish restricted diffusion due to seizure activity from that seen during an acute ischemic stroke: (1) The area of abnormality may not correspond to a typical vascular distribution; (2) there is frequently associated sulcal effacement and mass effect, earlier than would be expected with an acute stroke; (3) the abnormalities are usually reversible; (4) there is usually normal or increased perfusion; (5) there may be gyral or leptomeningeal enhancement on postcontrast images earlier than would be expected for an acute infarct; and (6) some reports of DWI changes in status epilepticus describe mixed diffusion findings with restricted diffusion in the cortex and elevated diffusion in the subcortical white matter, a pattern that would be unusual for acute ischemic stroke [151, 153, 157]. Occasionally, areas of chronic infarction may serve as seizure foci and present with DWI hyperintensity around the infarct area [152] that may be difficult to distinguish from an acute or chronic infarction in the absence of prior and follow-up imaging. In addition, a few reports describe transiently decreased diffusion in the corpus callosum in patients with a recent seizure, particularly involving the splenium [158, 159]. However, it should be noted that treatment with certain antiseizure medications...
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and withdrawal from these medications can also be associated with a transient splenial abnormality in patients without seizures (discussed later). Restricted diffusion in the cerebellar hemisphere contralateral to an area of supratentorial restricted diffusion in a crossed-cerebellar diaschisis pattern has also been described [154, 160].

Areas of diminished diffusion after seizures frequently resolve on follow-up. However, occasionally they can evolve into areas with increased ADC and T2 prolongation consistent with tissue damage, particularly in the hippocampus (Fig. 2.18) [149, 154, 155, 157, 161, 162]. Furthermore, initial MRI scans of patients with temporal lobe epilepsy can also have elevated ADC in the hippocampi [163], and hippocampal sclerosis has been associated with increased ADC and a lower anisotropy index [164]. Some investigators have found increased ADC in ipsilateral and contralateral hippocampi (compared to control subjects) on interictal scans of patients with temporal lobe epilepsy without evidence of hippocampal sclerosis on conventional imaging, although the ADC alone did not appear to provide any lateralizing information [165, 166]. Diffusion tensor imaging (DTI) is a

Table 2.8 Hemiplegic migraine

| Rare migraine subtype characterized by transient hemiparesis |
| Occasional patients with prolonged hemiplegic migraine have FLAIR hyperintensity, DWI hyperintensity, and restricted diffusion |
| Factors that help distinguish hemiplegic migraine from an acute arterial infarct |
| Strong history of migraines |
| Lesions may cover multiple arterial territories |
| Perfusion is normal or elevated |
| Absence of vascular occlusion |
| Lesions and clinical deficits are usually reversible |

| FLAIR hyperintensity, DWI hyperintensity, and restricted diffusion |

Fig. 2.16 Diffusion changes in a patient with hemiplegic migraine. (a–c) Axial FLAIR images demonstrate mild gyral FLAIR hyperintensity in the left parietal and posterior frontal lobes. (d–f) On diffusion maps, there is mild cortical and subcortical DWI hyperintensity (arrows in (d–f)), with (g–i) corresponding hypointensity on the ADC maps consistent with restricted diffusion. The diffusion changes resolved on a follow-up scan performed 3 days later although the FLAIR hyperintensity persisted (not shown).
promising tool for evaluation of microstructural changes in epileptic patients and white matter tracts involved in the epileptic network [167, 168]. DTI is discussed in a separate chapter.

**Metabolic, Toxic, and Drug-Induced Encephalopathies**

A wide variety of metabolic, toxic, and drug-induced encephalopathies can present with areas of T2 prolongation and diffusion abnormality on brain MRI. Their imaging appearance in isolation is typically not pathognomonic for a particular cause, but one clue to the presence of a more generalized metabolic or toxic etiology rather than an ischemic infarct is the presence of relatively symmetric bilateral patchy abnormalities not

![Fig. 2.17](image1) Diffusion changes associated with seizures. (a) Axial DWI and (b) ADC maps demonstrate cortical and subcortical DWI hyperintensity in the left parietal and posterior frontal lobes with minimal corresponding hyperintensity on the ADC map. The findings resolved on follow-up imaging (*not shown*)

![Fig. 2.18](image2) Diffusion changes associated with seizures. (a) Axial FLAIR, (b) DWI, and (c) ADC images demonstrate FLAIR hyperintensity with restricted diffusion in the right hippocampal formation (*black arrow* in a–c). (d) On follow-up exam performed 2 months later, the right hippocampal formation is hyperintense on the ADC map consistent with elevated diffusion secondary to alterations in tissue microstructure (*short wide arrows*). There was progression to a mesial temporal sclerosis pattern of volume loss and T2 prolongation on conventional MR images (*not shown*). The DWI hyperintensity in the left temporal lobe represents susceptibility artifact from the adjacent petrous temporal bone (*white arrow* in (b))

<table>
<thead>
<tr>
<th><strong>Table 2.9</strong> Diffusion changes associated with seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transiently restricted diffusion typically involving the cortex and subcortical white matter, the hippocampus, and the splenium of the corpus callosum</td>
</tr>
<tr>
<td>Diffusion changes may evolve into an area of T2 prolongation secondary to gliosis, particularly in the hippocampus</td>
</tr>
<tr>
<td>Patients with temporal lobe epilepsy can have elevated ADC values and loss of anisotropy in their hippocampi compared to control subjects, sometimes before the presence of a detectable abnormality on T2 or FLAIR images</td>
</tr>
<tr>
<td>Factors that help distinguish restricted diffusion due to seizure activity from an acute arterial infarct</td>
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<tr>
<td>Lesions may cover multiple arterial vascular territories</td>
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<tr>
<td>Mass effect earlier than would be expected for an acute stroke</td>
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<tr>
<td>Perfusion is normal or elevated</td>
</tr>
<tr>
<td>Absence of vascular occlusion</td>
</tr>
<tr>
<td>Gyral and leptomeningeal enhancement earlier than would be expected for an acute stroke</td>
</tr>
<tr>
<td>Lesions may be reversible</td>
</tr>
<tr>
<td>Presence of mixed diffusion with restricted diffusion in the cortex and elevated diffusion in the subcortical white matter, a pattern that would be unusual for an acute ischemic infarct</td>
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</table>
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 confined to a particular arterial distribution. Involvement of the splenium of the corpus callosum has also been described in toxic and metabolic encephalopathies (Table 2.10), either in isolation or in combination with other lesions. Although this is not specific for any one disorder, the splenium is an unusual site for an acute infarct secondary to arterial occlusion and its presence should alert the radiologist to the possibility of a nonischemic process. Similar to other entities that may mimic an acute stroke, the absence of significant stenosis on vascular imaging and normal or increased perfusion are also helpful in distinguishing toxic and metabolic encephalopathies from an acute stroke. This section provides a brief overview of the diffusion changes seen in these disorders.

### Hypoglycemia

Severe hypoglycemia can have a variety of clinical presentations ranging from a focal neurologic deficit mimicking an acute stroke to hypoglycemic coma. On MRI, severe hypoglycemia can be associated with bilateral and widespread areas of T2 prolongation with restricted diffusion that can involve the splenium of corpus callosum, cortex, and subcortical white matter (with a predilection for the occipital lobes and hippocampi), basal ganglia, internal capsules, brainstem, and middle cerebellar peduncles [169–175] (Fig. 2.19, Table 2.11). Depending on the severity and duration of hypoglycemia, the lesions can be reversible or evolve into areas of permanent T2 prolongation secondary to tissue

<table>
<thead>
<tr>
<th>Table 2.10</th>
<th>Causes of a splenial lesion on T2-weighted and DWI images</th>
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<tbody>
<tr>
<td>Antiepileptic drug treatment or withdrawal</td>
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<tr>
<td>Seizureb</td>
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<tr>
<td>Hypoglycemia</td>
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<tr>
<td>Trauma</td>
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<td>Marchiafava–Bignami disease</td>
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<td>Wernicke's encephalopathy</td>
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<td>Viral encephalitis</td>
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<td>Radiation therapy</td>
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<td>Hypermagnesemia and osmotic myelinolysis</td>
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<td>Hemolytic uremic syndrome</td>
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<td>Altitude sickness</td>
<td></td>
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<tr>
<td>Sympathomimetic-induced kaleidoscopic visual illusion</td>
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</tbody>
</table>

bThe splenial lesion may be isolated or part of a more widespread lesion pattern

bBecause seizure patients with splenial abnormalities typically either were on antiepileptic medications or had been recently taken off such medications, it is difficult to attribute the changes to seizures rather than the medications with certainty

<table>
<thead>
<tr>
<th>Table 2.11</th>
<th>DWI findings in metabolic, toxic, and drug-induced encephalopathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypoglycemia</td>
<td>Bilateral areas of T2 prolongation and restricted diffusion that can involve the splenium of the corpus callosum, cortex and subcortical white matter, hippocampi, basal ganglia, internal capsules, and posterior fossa structures</td>
</tr>
<tr>
<td></td>
<td>Predilection for the occipital lobes and splenium</td>
</tr>
<tr>
<td></td>
<td>Cause of restricted diffusion – cytotoxic edema</td>
</tr>
</tbody>
</table>

(continued)
damage and gliosis [169, 171, 174, 176]. In cases of isolated lesions involving a single vascular territory, distinction from an ischemic infarct may not be possible without additional clinical information or follow-up [170].

**Heroin Inhalation Leukoencephalopathy**

Inhalation of heroin vapor, sometimes referred to as “chasing the dragon,” can result in a rare form of toxic leukoencephalopathy with extensive abnormalities on MRI [177, 178] (Fig. 2.20, Table 2.11). HIL can present as marked symmetric areas of white matter T2 prolongation. In the cerebrum, the occipital lobes are most extensively involved with progressive involvement of the parietal, temporal, and frontal lobes [178]. The splenium of the corpus callosum and cerebellum can also be affected. In addition, there can be symmetric involvement of the corticospinal tracts, medial lemniscus, and tractus solitarius. There are limited descriptions of diffusion changes in the areas of white matter signal abnormality but both restricted diffusion and elevated diffusion have been described, probably depending in part on the time lag between the onset of the encephalopathy and time at which the MRI was performed. Acute lesions can have decreased diffusion.

**Metronidazole-Induced Encephalopathy**

Metronidazole is a widely used 5-nitroimidazole antibiotic that can be associated with a number of neurologic side effects including peripheral neuropathy, encephalopathy, cerebellar dysfunction, and seizures. Metronidazole-induced encephalopathy is rare. Typically, patients have bilateral and symmetric patchy T2 hyperintense lesions involving the dentate nuclei of the cerebellum, with less frequent involvement
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of subcortical white matter, the corpus callosum, and various other brainstem structures [179–183] (Fig. 2.21, Table 2.11). Lesions are usually hyperintense on DWI but may have restricted diffusion or be isointense or hyperintense on the ADC map [180–183]. The lesions are typically reversible, although there are reports of residual T2 prolongation on short-term follow-up MRI, especially in the corpus callosum [180–183].

Carbon Monoxide Poisoning

Acute carbon monoxide (CO) toxicity can result in multifocal areas of T2 prolongation with restricted diffusion on MRI [184, 185] (Table 2.11). There is a predilection for involvement of the globus pallidus alone in mild cases. In more severe cases, the remainder of the deep gray nuclei and the deep white matter and cortex, especially the hippocampus, can be affected.

Fig. 2.20 MR images from a 23-year-old man found unresponsive after heroin inhalation. (a–d) Axial FLAIR images demonstrate extensive hyperintensity in the subcortical white matter, corona radiata, posterior limb of the internal capsule, and corticospinal tracts. (e–h) The majority of the lesions are hyperintense on DWI and (i–l) hypointense on ADC maps, consistent with restricted diffusion. This pattern is compatible with severe heroin inhalation injury. Additional foci of signal abnormality in the lentiform nucleus and hippocampal formations are nonspecific but, may represent a component of anoxic brain injury.
In addition, although less commonly identified on MRI, lesions may also be present in the substantia nigra and when combined with lesions in the globi pallidi, are referred to as a pallidoreticular pattern of injury [184, 186]. In addition to lesions seen after recent CO toxicity, patients with CO poisoning can also present with a delayed encephalopathy consisting of extensive T2 hyperintense white matter lesions that may also at least in part demonstrate decreased diffusion [184, 187].

Osmotic Myelinolysis Syndromes

Osmotic myelinolysis is a neurologic disease caused by severe damage of the myelin sheath due to rapid correction of hyponatremia, frequently associated with alcoholism. Lesions are typically seen in the pons (pontine myelinolysis) but can also be seen in other structures (extrapontine myelinolysis) such as the cerebellum, cerebral peduncles, basal ganglia, internal capsules, and other white matter tracts (Table 2.11). The lesions are T2 hyperintense and relatively symmetric, and may present with either restricted or elevated diffusion, probably depending on the timing of imaging in relation to symptom onset [188–190].

Other Syndromes Associated with Alcoholism

Wernicke’s encephalopathy results from inadequate intake or absorption of thiamine and is characterized by ataxia, ophthalmoplegia, confusion, and impairment of short-term memory. On MRI, symmetric T2 prolongation with transient restricted diffusion of the medial thalami, periaqueductal gray, and mamillary bodies has been reported [191]. A case report also describes restricted diffusion in the splenium of corpus callosum [192]. Marchiafava–Bignami disease, a rare progressive neurologic disease associated with chronic alcoholism, can also present with T2 prolongation and/or restricted diffusion in the corpus callosum, cerebral cortices, internal capsule, and the thalamus [193–195]. The callosal lesion typically involves the splenium but may also involve the body of the corpus callosum [193–196].

Other Drugs and Metabolic Conditions Associated with Restricted Diffusion

In addition to the entities previously discussed, a number of other toxic, metabolic, or drug-related conditions may present with T2 prolongation and restricted diffusion, particularly involving the splenium of the corpus callosum [197]. These include treatment with antiseizure medications [198, 199] (Fig. 2.22), withdrawal of antiseizure medications [200, 201],

Fig. 2.21 Metronidazole-induced encephalopathy. (a, b) Axial FLAIR and (c, d) ADC images demonstrate bilateral symmetric FLAIR hyperintensity involving the cerebellar dentate nuclei. On the ADC map, the lesions are hyperintense consistent with elevated diffusion. The lesions were isointense on DWI (not shown). On follow-up after discontinuation of the medication, all abnormalities resolved (not shown). Lesions associated with metronidazole toxicity can also have restricted diffusion

Fig. 2.22 Transient splenial lesion associated with antiepileptic medication (valproic acid) treatment. (a) Axial DWI and (b) ADC images from a 16-year-old girl treated with antiepileptic medications for psychiatric illness and no history of seizures demonstrate restricted diffusion in the splenium of the corpus callosum. The abnormality resolved on follow-up MRI after discontinuation of the medication (not shown)
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sympathomimetic-induced kaleidoscopic visual illusion syndrome [202], hemolytic uremic syndrome, and high altitude brain injury (Table 2.10). There are a few reports of DWI abnormalities in patients with severe hemolytic uremic syndrome. These patients can have restricted diffusion and/or T2 prolongation in the basal ganglia, especially the dorsolateral lentiform nucleus with less frequent involvement of the thalamus, cerebellum, and brainstem [203, 204]. Depending on the severity of disease, the lesions may or may not be reversible [203–205]. One case report also describes a focal T2 hyperintense lesion in the splenium of the corpus callosum, but diffusion-weighted images were not performed [205]. Acute high altitude sickness can also be associated with DWI abnormalities. In a simulated study of acute high altitude sickness by exposure to normobaric hypoxia, some patients had decreased ADC values in the splenium of the corpus callosum in addition to mild generalized increase in cerebral volume and edema [206]. One case report describes a T2 hyperintense lesion with elevated ADC in the splenium of the corpus callosum, but the MRI was performed 14 days after symptom onset [207].

Inflammatory Demyelinating Lesions

Numerous investigations have demonstrated diffusion changes in acute and chronic demyelinating lesions [208–213]. Although acute enhancing lesions in MS or acute disseminated encephalomyelitis most frequently have elevated diffusion, they can have transiently restricted diffusion at their periphery or even in their core, usually attributed to cytotoxic edema, fluid shifts between IC and EC compartments, or dense inflammatory cell infiltration [208–210, 212–214] (Fig. 2.23, Table 2.12). Therefore, a demyelinating lesion should always be considered in a patient presenting with an acute neurologic deficit and a small lesion with restricted diffusion in an atypical location, atypical pattern, or an atypical age group for an ischemic stroke. A ring pattern of restricted diffusion has also been described in cases of tumefactive demyelinating lesions (TDL). In one retrospective analysis of 18 cases of TDLs, 11 patients (61%) had lesions with increased ADC.

**Table 2.12 Demyelinating lesions**

| Acute demyelinating lesions in multiple sclerosis or acute disseminated encephalomyelitis typically have elevated diffusion |
| Less commonly, acute lesions have decreased diffusion in both enhancing and nonenhancing lesions |
| Cause of restricted diffusion: cytotoxic edema, fluid shifts between IC and EC compartments, or dense inflammatory cell infiltration |
| Tumefactive demyelinating lesions are frequently rim enhancing with restricted diffusion in the rim and elevated diffusion in the center of the lesion |
| Chronic lesions typically have elevated diffusion with the greatest diffusivity seen in T1 hypointense lesions, which correspond to areas of severe tissue destruction |
| A single lesion with restricted diffusion can be mistaken for an acute infarction |

Fig. 2.23 Different appearances of enhancing demyelinating lesions on DWI. (a, b) Axial contrast-enhanced T1-weighted images from a patient with multiple sclerosis demonstrate two enhancing lesions located in the left temporo-parietal region and at the junction of the left middle cerebellar peduncle and lower pons. (c, d) Although both lesions are hyperintense on DWI, (e, f) the supratentorial lesion is mildly hyperintense on ADC whereas the infratentorial lesion is mildly hypointense on ADC. Demyelinating plaques most frequently have normal or elevated diffusion but less commonly have diminished diffusion and can be misdiagnosed as ischemic infarcts. Incidentally, there is a right middle cranial fossa arachnoid cyst.
in the center and peripheral restricted diffusion either as a complete or an incomplete ring, 5 had increased ADC without evidence of peripheral diffusion restriction, and 2 had peripheral restriction without increased ADC in the center of the lesion [215]. Therefore, DWI in conjunction with conventional MR sequences and MR spectroscopy may be helpful in distinguishing TDLs from neoplasms. On DWI, chronic T2 hyperintense MS lesions usually demonstrate elevated diffusion with the greatest diffusivity seen in T1 hypointense lesions, which correspond to areas of severe tissue destruction and cavitation [208, 212, 216].

DTI is widely used in MS research. Changes in diffusion anisotropy correlate with demyelination and axonal loss, and DTI can reveal alterations in tissue microstructure that may not be apparent on conventional MR sequences or conventional DWI. Potential applications of DTI that are under investigation include its use for quantification of the severity of degenerative neuronal/axonal change, additional characterization of T2 hyperintense lesions, identification of abnormalities within normal appearing white matter on conventional MR sequences, and mapping structural connectivity among brain regions [211, 217, 218]. A detailed discussion of applications of DTI in demyelinating disease is beyond the scope of this chapter but can be found elsewhere in this book and in review articles on the topic [211, 217–219].

Cerebral Infections

Abscesses

DWI is a very useful adjunctive MR sequence for the evaluation of ring enhancing brain lesions and allows reliable distinction of a pyogenic brain abscess from a necrotic tumor. Pus within the central core of a pyogenic brain abscess restricts diffusion and is typically homogeneously hyperintense on DWI with a low ADC value (Fig. 2.24, Table 2.13). On the contrary, the necrotic or cystic component of a tumor tends to have elevated diffusion with intermediate intensity on DWI and hyperintensity on ADC maps [220–223]. However, it should be noted that treated abscesses tend to have a more heterogeneous appearance depending on the stage and response to treatment, and can contain mixed areas of restricted and elevated diffusion [224]. In fact, DWI can be useful for follow-up of pyogenic abscesses. In small studies, decreasing DWI hyperintensity and increasing ADC value within purulent collections, including intraparenchymal

Table 2.13 Cerebral infections

<table>
<thead>
<tr>
<th>Pyogenic infections</th>
<th>Nonpyogenic abscesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyogenic collections have homogeneously restricted diffusion due to increased viscosity of pus</td>
<td>These abscesses have a more variable and heterogeneous appearance with areas of diminished diffusion, elevated diffusion, or both</td>
</tr>
<tr>
<td>Ring enhancing lesions with homogeneously restricted central diffusion are almost always pyogenic abscesses</td>
<td>Viral encephalitis</td>
</tr>
<tr>
<td>Subdural empyemas and subdural effusions appear similar on conventional sequences. Empyemas have homogeneously restricted diffusion, while effusions have elevated diffusion</td>
<td>Can have restricted diffusion acutely, especially involving the cortex and subcortical white matter</td>
</tr>
<tr>
<td>DWI improves the detection of ventriculitis with intraventricular pus</td>
<td>The lesions may be more conspicuous on DWI compared to T2 weighted or FLAIR images</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Creutzfeldt-Jacob disease</th>
<th>Regions with restricted diffusion are more likely to lead to irreversible neuronal damage and are associated with poor outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV 1 lesions have a predilection for the limbic system – the medial temporal lobes, insula, cingulate gyri, and subfrontal regions</td>
<td>HSV 1 lesions have a predilection for the limbic system – the medial temporal lobes, insula, cingulate gyri, and subfrontal regions</td>
</tr>
<tr>
<td>DWI is more sensitive than FLAIR or T2 weighted images for lesion detection</td>
<td>Restricted diffusion can persist for a long time in some cases</td>
</tr>
</tbody>
</table>

Fig. 2.24 Bacterial abscess. (a) Axial contrast-enhanced T1, (b) DWI, and (c) ADC images demonstrate a large ring enhancing lesion in the left frontal lobe with marked associated vasogenic edema (demonstrating elevated diffusion), mass-effect, and midline shift. There is homogeneously restricted diffusion within the lesion, a finding highly suggestive of an abscess.
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abscesses and extra-axial collections, has been shown to correlate with treatment response clinically [224–227].

Nonpyogenic abscesses have a more variable appearance. Tuberculous abscesses frequently have restricted diffusion in their core and/or wall, similar to pyogenic abscesses [222]. On the contrary, fungal abscesses commonly are heterogeneous with mixed areas of restricted diffusion or with elevated diffusion within the central cavity and restricted diffusion in the abscess wall [222, 228]. Fungal abscesses can also have irregular projections with diminished diffusion corresponding to inflammatory tissue and fungal hyphae [222]. Restricted diffusion within an abscess should not be confused with infarcts secondary to angioinvasive or embolic infections as may occur with aspergillosis or tuberculosis, which are usually distinguishable based on other imaging characteristics.

Toxoplasma abscesses can have a mildly hyperintense core on DWI that is usually isointense or hyperintense to normal brain parenchyma on ADC [229] (Fig. 2.25). Similar to fungal infections, evaluation of the abscess wall may be helpful. In one report of four cases, all had a low ADC value in the abscess wall [229]. In another study of acquired immunodeficiency syndrome (AIDS) patients, toxoplasma abscesses typically had higher ADC values than lymphoma, an important differential consideration in that patient population, and only toxoplasma abscesses had a lesion to normal white matter ADC ratio greater than 1.6 [230]. However, other studies have described greater overlap in lesion ADC values [231], and in many cases a definitive distinction may not be possible.

Meningitis

The diagnosis of meningitis remains primarily a clinical one, but imaging plays an important role in excluding other CNS lesions and may, in addition, demonstrate signs supporting a diagnosis of meningitis. Sulcal restricted diffusion is sometimes seen in cases of bacterial meningitis [227], but DWI is not nearly as sensitive as FLAIR for detection of meningeal abnormalities. However, DWI is excellent for detection of complications of meningitis (Fig. 2.26). For example, DWI is highly sensitive for detection of pyogenic ventriculitis.

Fig. 2.25 Toxoplasma abscess. (a) Axial contrast-enhanced T1, (b) DWI, (c) ADC, and (d) exponential images demonstrate a ring enhancing lesion centered in the posterior putamen with associated vasogenic edema and mass effect. On diffusion maps, the lesion is heterogenous with regions of mildly restricted diffusion and elevated diffusion. There is mildly restricted diffusion in the abscess wall, a feature that may be helpful in characterization of these lesions and has also been described in fungal abscesses

Fig. 2.26 Meningitis and complications. (a) Axial contrast-enhanced T1, (b, c) DWI, and (d) ADC images from a 4-month-old girl with Staphylococcus aureus meningitis are shown. On the postcontrast T1 image, there is diffuse meningeal enhancement. DWI and ADC maps demonstrate small foci of purulent debris in the right frontal subarachnoid space (arrow in (b) and (d)) and in the prepontine cistern and cerebellopontine angle (arrow in (c)). In this case, the patient responded to conservative treatment with antimicrobial therapy
Intraventricular pus, similar to pus within an abscess, has restricted diffusion and is markedly hyperintense on DWI. The debris is typically located in a dependent position in the trigones or occipital horns of the lateral ventricles or, less commonly, the fourth ventricle [232–235]. Furthermore, DWI can differentiate subdural empyemas from subdural effusions. Both are T1 hypointense and T2 hyperintense, but empyemas have restricted diffusion while simple effusions have elevated diffusion. Lastly, DWI improves the detection of arterial infarctions due to meningitis-associated vasculitis and of venous infarctions due to associated venous sinus thrombosis.

### Encephalitis

Encephalitis is an acute infection of the brain parenchyma characterized clinically by headache, fever, and altered mental status. Viral encephalitis has been associated with more than 100 viruses and its diagnosis requires a combination of clinical findings, serologic and cerebrospinal fluid (CSF) laboratory analysis, and imaging. Although a thorough discussion of the variety of MR patterns seen in viral encephalitis is beyond the scope of this chapter, diffusion findings in a few common encephalitides are discussed to illustrate the adjunctive role of DWI for their characterization. One common feature shared by many viral encephalitides is the presence of restricted diffusion in regions of T2 prolongation during the acute stage (Table 2.13). Occasionally, lesions may be more conspicuous on DWI compared to T2 and FLAIR images [236–240].

Herpes encephalitis is the most common cause of acute fatal sporadic encephalitis in humans [237]. The majority of infections in adults are secondary to herpes simplex type 1 (HSV-1). HSV-1 has a predilection for limbic system structures including the medial temporal lobes, the insula, the subfrontal areas, and the cingulate gyri (Fig. 2.27). Both restricted diffusion from cytotoxic edema and elevated diffusion from vasogenic edema may be seen during the acute phase of herpes simplex encephalitis and the two patterns are frequently present concurrently [236, 237, 241, 242]. In general, areas with restricted diffusion are believed to be more likely to lead to irreversible neuronal damage and are associated with poor clinical outcomes [237, 241]. In some cases, acute lesions may be better visualized on DWI compared to FLAIR or T2-weighted images [236, 237]. Chronically, the lesions tend to demonstrate elevated ADC, similar to parenchymal injury from other causes.

HSV-2 encephalitis is much less common than HSV-1 encephalitis and typically affects neonates. HSV-2 does not have the temporal lobe predilection seen with HSV-1 and may present with patchy areas of T2 hyperintense signal abnormality throughout the cerebral hemispheres and deep gray nuclei. These areas typically have restricted diffusion during the acute phase and progress to cystic encephalomalacia with elevated diffusion in the chronic stage [239].

In addition to the human herpes virus family, a large number of nonherpetic viruses can result in meningoencephalitis. These include Japanese encephalitis, a mosquito-borne flaviviral encephalomyelitis, different forms of measles encephalitis, and enteroviral encephalitis, among others [243]. DWI can demonstrate multifocal areas of restricted diffusion involving the cortex, subcortical white matter, and deep gray nuclei during the acute phase of these diseases and is useful for distinguishing areas of cytotoxic edema from vasogenic edema [243]. The specific patterns of T2 prolongation and diffusion change in nonherpetic and other viral encephalitides can be found in primary articles and reviews on the topic [243–246]. Viral encephalitis can also present with, and is on the differential diagnosis for, a reversible splenial lesion [246, 247] (Table 2.10).

### Creutzfeldt-Jacob Disease

Creutzfeldt-Jacob disease (CJD) is a rare rapidly progressing and ultimately fatal dementing illness caused by infection from an isoform of the prion protein with an incidence of less than one per million [248, 249]. CJD can be sporadic (from spontaneous mutations), familial (hereditary), or acquired and MRI with DWI is the optimal imaging modality for demonstration of intracranial lesions. In the sporadic form, there are typically symmetric areas of diffusion change with or without T2 prolongation in the basal ganglia, especially the corpus striatum [248–252] (Fig. 2.28, Table 2.13). In addition, symmetric or asymmetric areas of cerebral or cerebellar cortical signal abnormality may be present with or
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without striatal involvement. Less common features include involvement of the periaqueductal gray matter, symmetric involvement of the thalami, asymmetric involvement of the corpus striatum, or involvement of the cerebellar cortex. The variant form of CJD shows a different pattern with symmetric involvement of the pulvinar and the dorsomedial thalamus in a high percentage of cases [249, 253]. However, the striatum, periaqueductal gray, and, less commonly, other areas may be affected similar to the sporadic form [249, 254, 255]. Cortical involvement is frequently not seen in the variant form [255].

DWI is more sensitive than conventional MR sequences for identification of lesions in CJD [249, 251, 256–260] and can demonstrate lesions even before development of periodic sharp wave complexes on EEG [261]. Lesions are typically hyperintense on DWI and frequently have low values on the ADC map due to restricted diffusion, although normal or even elevated ADC may occasionally be present, possibly related to the duration of disease and time before imaging [249, 255–258, 261]. Although there is some conflicting data on correlation of MR findings with findings on postmortem pathology, many studies have demonstrated that regions with decreased ADC correlate with spongiform change [251, 259, 260]. On follow-up imaging, there can be persistent, or even an increase in, restricted diffusion over periods lasting weeks to months in some patients, but in others there is an eventual

**Fig. 2.28** Sporadic Creutzfeldt-Jacob disease (CJD). (a–c) Axial FLAIR. (d–f) DWI, and (g–i) ADC images are shown. On the FLAIR images, there is subtle fairly symmetric hyperintensity involving the corpus striatum, the thalami, the anterior frontal cortex, the cingulate gyri, and the insula. The abnormalities are much better visualized on the DWI images due to increased lesion contrast. The abnormalities are hypointense to isointense on the ADC maps.

![Brain images](image-url)
decrease in DWI intensity and increase in ADC value [252, 256, 261–263]. In addition, different lesions in the same patient may evolve differently [261, 262]. In one study, diffusion changes were better visualized on DWI images obtained at a higher $b$-value (3,000 s/mm$^2$) compared to standard DWI (1,000 s/mm$^2$), although no new areas of involvement were identified on the high $b$-value images [255]. In addition, the authors found that while the abnormalities in sporadic CJHD had predominantly low ADC, including in the thalamus, there was elevated ADC in the pulvinar in variant CJD and this finding may provide an additional useful feature for distinction from sporadic CJD [255].

Neoplasms

DWI is an important adjunctive sequence in the evaluation of both intra-axial and extra-axial brain tumors (Table 2.14). DWI provides important additional information that helps distinguish neoplasms from cerebral abscesses and TDL. In addition, DWI can provide additional information on tumor characteristics such as cellularity. In general, the ADC value is inversely proportional to cellular density of a mass and tumors with high cellularity and densely packed cells tend to exhibit relatively diminished diffusion [264–266]. In certain tumors such as epidermoids, the DWI signature in combination with signal characteristics on conventional sequences is essentially pathognomonic. It should be noted that since the signal intensity of DWI images relies on a number of factors including T2 effects, there can be marked variability in tumor appearance on the DWI image. Therefore, many studies of diffusion characteristics of tumors focus on the ADC map instead.

Table 2.14  DWI for intracranial neoplasms

<table>
<thead>
<tr>
<th>Glial neoplasms and intracranial metastases</th>
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<tbody>
<tr>
<td>Solid portions of higher grade tumors tend to have a lower ADC value compared to lower grade tumors</td>
</tr>
<tr>
<td>ADC usually increases after successful treatment</td>
</tr>
<tr>
<td>Recurrent neoplasms tend to have lower ADC compared to areas of treatment change</td>
</tr>
<tr>
<td>Peritumoral “edema” of high-grade glial neoplasms tends to have lower ADC compared to peritumoral “edema” of low-grade glial neoplasms or metastases</td>
</tr>
<tr>
<td>DWI characteristics cannot reliably distinguish between high-grade and low-grade tumors or between recurrent tumor compared to treatment change because of significant overlap but can be useful as an adjunctive sequence in combination with conventional MR sequences, MR spectroscopy, and MR perfusion</td>
</tr>
<tr>
<td>CNS lymphoma</td>
</tr>
<tr>
<td>Lymphomas usually have relatively homogeneously decreased diffusion</td>
</tr>
<tr>
<td>Homogeneously enhancing intra-axial lesions with decreased diffusion usually represent lymphomas</td>
</tr>
<tr>
<td>Lower pretreatment ADC values are associated with shorter disease-free and overall survival</td>
</tr>
<tr>
<td>Extra-axial masses</td>
</tr>
<tr>
<td>Epidermoid tumors can be readily distinguished from an arachnoid cyst with DWI. Arachnoid cysts have elevated diffusion, similar to CSF, and are dark on DWI images. Epidermoids have diffusion similar to normal brain tissue and are markedly hyperintense on DWI due to their diffusion and T2 characteristics</td>
</tr>
<tr>
<td>Malignant or atypical meningiomas have lower ADC values than typical meningiomas</td>
</tr>
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</table>

Primary Glial Neoplasms and Intracranial Metastases

Tumors of glial origin or astrocytomas constitute the most common primary intra-axial neoplasm in adults. Although the ADC of high-grade astrocytomas tends to be lower than low-grade astrocytomas, there is significant variability and overlap between the diffusion characteristics of high- and low-grade neoplasms and the reported accuracy of ADC for prediction of tumor grade [264, 267–271] (Fig. 2.29). Within a tumor, the cystic areas tend to have higher diffusivity/ADC values [268] (Fig. 2.29). Selective analysis of solid tumor areas may help improve accuracy of ADC in predicting tumor cellularity and grade, but even when only the solid portion or darkest area on ADC is used for analysis, there is marked variation in the ADC values [269–272]. For example, when the reported ADC values from three studies that found a difference between high-grade and low-grade malignant tumors are combined, the mean ADC values for high-grade tumors are between 520 to $1,130 \times 10^{-6}$ mm$^2$/s compared to 1,010 to $1,350 \times 10^{-6}$ mm$^2$/s for low-grade tumors, with much greater variation between the ADC of individual cases [269–271]. Furthermore, there are no universally accepted standardized methods for selecting subsites, and the ADC cannot be used to reliably predict tumor grade from a practical clinical perspective. Similar to adult brain tumors, high-grade malignant pediatric brain tumors tend to have diminished diffusion compared to low-grade tumors and some studies have reported high sensitivity and specificity of DWI in this regard [273] that require confirmation in larger studies.

Intracranial metastases typically have elevated diffusion with variable ADC values and cannot be distinguished from malignant gliomas based on diffusion characteristics alone.
Increased cellularity and higher grade of malignant intracranial metastases tend to correlate inversely with the tumor ADC values, but similar to primary brain tumors there is substantial variability and overlap between low-grade and high-grade tumors and between metastases and primary brain tumors [272, 274]. Some studies have found that analysis of ADC of peritumoral “edema” can be helpful for distinguishing different tumor types. For the sake of simplicity, we use the term edema, although we prefer the designation “T2/FLAIR hyperintensity” given the well-known fact that what is called “peritumoral edema” typically has a significant component of neoplastic cells in cases of primary brain neoplasms. In one study, diffusivity was higher in peritumoral “edema” associated with primary neoplasms and metastases compared to normal white matter, but the ADC tended to be lower in areas of T2/FLAIR hyperintensity associated with high-grade astrocytomas compared to metastases [275]. Some, but not all, studies have also found that ADC values are higher in peritumoral “edema” associated with low-grade compared to high-grade gliomas [269, 271, 275]. However, there is overlap in ADC values and diffusion changes in isolation cannot reliably distinguish between peritumoral “edema” associated with high-grade and low-grade primary tumors or metastases.

DWI has also been used to evaluate tumor response to therapy. In both animal studies and humans, an increase in tumor ADC tends to correlate with response to therapy in primary and metastatic CNS neoplasms and a reduction in ADC may be seen with tumor recurrence [266, 276–283]. In addition, changes in ADC may precede the changes in lesion volume on conventional sequences and may provide an early indicator of tumor response to therapy. Image acquisition at higher \( b \)-values has also been shown to increase sensitivity for detection of diffusion changes following treatment [278]. With continued research and development of more sophisticated computer-aided methods of analysis, DWI has the potential to emerge as an important adjunctive sequence and early biomarker for evaluation of tumor response to therapy [280–282, 284].

In addition to assessing response to therapy, some studies suggest that DWI may be useful for distinguishing tumor recurrence from radiation necrosis and other treatment-related changes. In one retrospective analysis of high-grade gliomas treated with radiation with or without chemotherapy, the mean ADC value of enhancing regions and their ADC ratio compared to normal contralateral white matter was lower in recurrent/progressive tumors compared to the treatment-related change group [283], and other investigators have reported similar observations [285, 286]. However, similar to studies using ADC values for distinguishing...
high-grade from low-grade tumors, there is substantial overlap in the ADC values of tumor recurrence and treatment-related change and there are reports of decreased diffusion in pathologically proven radiation necrosis [287, 288]. Even though DWI alone is frequently not sufficient for distinguishing between the two, analysis of ADC changes is helpful when used in combination with other parameters such as perfusion characteristics and MR spectroscopy [285, 287]. A discussion of MR perfusion and spectroscopy is beyond the scope of this chapter but can be found elsewhere in this book.

DWI can also be useful in the evaluation of patients treated with antiangiogenic therapy. In a recent study of patients with high-grade gliomas treated with bevacizumab alone or in combination with other chemotherapeutic agents, the authors found that patients with progressive tumor had a decline in the ADC values of the enhancing as well as non-enhancing components [289]. In this study, there was no significant change in the ADC values of tumors that did not progress, although there was a trend toward increased ADC on follow-up in this group.

DTI is also being investigated for evaluation of radiation change within normal brain parenchyma. Interestingly, there are some contradictory results compared to those with conventional DWI as some have reported an increase in the ADC of the contrast-enhancing component in patients with tumor recurrence [290, 291]. This requires further investigation but may at least in part be related to differences in study design and time from treatment, given that in one DTI study the interval from treatment was much longer, ranging from many months to years after completion of therapy [290].

**Lymphoma**

CNS lymphoma is typically isointense to hypointense on T1- and T2-weighted images, enhances homogeneously and has homogeneously restricted diffusion due to relatively dense cell packing [230, 292, 293] (Fig. 2.30). This diffusion pattern is unusual for other primary and secondary CNS neoplasms and can be used to suggest the diagnosis. In immunocompromised patients, the diminished diffusion within lymphoma can be helpful for distinction from toxoplasmosis, which tends to have more variable ADC, although some studies have found significant overlap in the DWI appearance of lymphoma and toxoplasmosis [229–231]. DWI may also be important in predicting outcome. Lower pretreatment ADC values within the

![Fig. 2.30 Lymphoma. (a, b) Axial T2 and (c, d) postcontrast T1-weighted images demonstrate multiple subependymal enhancing lesions that have relatively low signal on T2 (arrows in (a) and (b)). (e, f) On DWI, the lesions are heterogeneous but partially bright. (g, h) On ADC, the lesions are hypointense consistent with restricted diffusion secondary to increased cellularity. The more superiorly located lesion had an average ADC value of approximately 600 × 10⁻⁶ mm²/s, whereas the two other lesions have average ADC values ranging between 800 and 850 × 10⁻⁶ mm²/s – all in the expected range for lymphoma](image-url)
enhancing portion of primary CNS lymphoma have been shown to be associated with shorter disease-free and overall survival [294].

**Extra-Axial Masses**

The role of DWI in distinction of epidermoid tumors from extra-axial cystic lesions, such as arachnoid cysts, is well established. Both arachnoid cysts and epidermoids have signal characteristics similar to CSF and are indistinguishable on T1- and T2-weighted sequences, although epidermoid cysts do have elevated signal compared to surrounding CSF on FLAIR images. On DWI, arachnoid cysts have diffusion characteristics similar to CSF (markedly hyperintense to brain parenchyma on ADC and hypointense on DWI images), while epidermoids are markedly hypointense to CSF and isointense to brain parenchyma on ADC maps and are markedly hyperintense to CSF and brain parenchyma on DWI images due to T2 components and diffusion characteristics similar to that of normal brain parenchyma [223, 295, 296] (Fig. 2.31).

A number of investigations have also evaluated the use of DWI for differentiation of malignant and atypical meningiomas from benign meningiomas [297–299]. In a recent retrospective study of 25 atypical/malignant and 23 benign meningiomas, the former were found to have significantly lower absolute and normalized ADC values compared to benign meningiomas [298]. Absolute ADC and normalized ADC thresholds of $800 \times 10^{-6}$ mm$^2$/s and 0.99, respectively, were found to have high sensitivity and specificity for distinguishing the two, but require validation in larger multicenter studies.

**Traumatic Brain Injury**

DWI is complementary to conventional MR sequences such as T2/FLAIR and T2* for identification of diffuse axonal injury (DAI) in acute closed-head injury [300, 301] (Fig. 2.32, Fig. 2.33).

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**Fig. 2.31** Epidermoid tumor. (a) Axial T2, (b) contrast-enhanced T1, (c) DWI, and (d) ADC images demonstrate an insinuating nonenhancing extraaxial lesion anterior to the lower pons and right middle cerebellar peduncle that has signal characteristics similar to CSF on T1- and T2-weighted sequences, but is markedly hyperintense to CSF on DWI images and hypointense to CSF on the ADC map. The lesion has diffusion similar to that of normal brain parenchyma but is hyperintense to brain parenchyma on the DWI images due to the combined diffusion and T2 effects. These findings are essentially pathognomonic for an epidermoid tumor.

**Fig. 2.32** Traumatic brain/shear injury. (a–d) Axial DWI images demonstrate punctate DWI hyperintense foci at frontal gray white matter junctions bilaterally as well as a lesion in the splenium of corpus callosum in this patient who was evaluated following a closed head injury.
is complementary to other MR sequences because it identifies nonhemorrhagic lesions not visible on T2* images and demonstrates nonhemorrhagic lesions with restricted diffusion better than FLAIR images because of increased lesion contrast [300]. The anatomic distribution of DWI

Table 2.15  DWI for evaluation of acute closed head injury

DWI is complementary to T2* and FLAIR images for evaluation of diffuse axonal injury and can identify additional lesions not detectable on these sequences

The majority of nonhemorrhagic lesions have restricted diffusion, secondary to ischemia and/or the formation of axonal retraction balls.

A small percentage is isointense or hyperintense on the ADC map, probably secondary to increased tissue water at discharge than volume of lesions on FLAIR, T2, T2* or all images, including DWI, combined

Higher ADC values in normal appearing brain parenchyma are associated with a poor clinical outcome

Table 2.16  Selected articles on diffusion imaging of the brain

<table>
<thead>
<tr>
<th>Authors</th>
<th>Title</th>
<th>Subjects</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mullins et al. 2002 [34]</td>
<td>CT and conventional diffusion-weighted MR imaging in acute stroke: study in 691 patients at presentation to the emergency department. Radiology 2002;224:353–60</td>
<td>691 acute stroke patients</td>
<td>Study comparing the diagnostic accuracy of CT, conventional MRI (without DWI), and MRI with DWI for the diagnosis of an acute ischemic stroke</td>
</tr>
<tr>
<td>Yoo et al. 2010 [99]</td>
<td>Combining acute DWI and MTT lesion volumes with NIHSS score improves the prediction of acute stroke outcome. Stroke 2010;41(8):1728–35.</td>
<td>Acute DWI and MTT lesions</td>
<td>An evaluation of the use of DWI and mean transit time in conjunction with NIHSS for prediction of stroke outcome</td>
</tr>
</tbody>
</table>
positive shear lesions is similar to that seen on conventional sequences, most commonly affecting the corticomedullary junction, followed by central white matter and the junction of the midbrain andpons. In one study, the volume of lesions identified on DWI had a better correlation with the modified Rankin scale (mRS) at discharge than volume of lesions on FLAIR, T2, T2* or all images, including DWI, combined [302]. In another study, ADC maps were used to detect DAI lesions not visible on other sequences [303]. In this study, ADC values in normal-appearing brain parenchyma were shown to be predictive of outcome with significantly higher mean deep gray and white matter ADC values in patients with unfavorable outcomes, defined as Glasgow Outcome Scale scores 1–3, compared to those with favorable outcomes and controls.

**Conclusion: Future Applications of Diffusion Imaging in the Brain**

Over the past 10 years, DWI has become a standard sequence for MR evaluation of ischemic and nonischemic central nervous system (CNS) lesions (see Table 2.16 for a summary of some important diffusion studies). Currently, DWI is the gold standard for evaluation of acute ischemic infarction and provides the best estimate of the infarct core. In addition, DWI is an important adjunctive sequence for characterization of a wide range of infectious, inflammatory, neoplastic, and traumatic brain lesions. DWI and ADC maps are increasingly used in clinical research for quantification of the irreversible infarct core, prediction of infarct complications such as hemorrhagic transformation, and evaluation of pseudo-progression and other treatment-related changes in tumor imaging. Although currently in the research phase, these parameters are likely to be implemented in the clinical arena in the near future. In the future, computer-assisted analysis may be used for subsite analysis of DWI, perfusion images, and MR spectroscopy as part of complex algorithms for patient stratification and prognostication in stroke imaging and to distinguish treatment-related changes from tumor progression in the evaluation of CNS astrocytomas. These provide exciting opportunities for additional research and the potential to further expand the role of DWI in diagnostic imaging of brain disorders in the next decade.

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