Diagnostic approach to restricted-diffusion patterns on MR imaging

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Summary

The vast majority of restricted-diffusion abnormalities result from acute stroke, and as such, the diagnosis may be problematic when this MRI feature results from other causes. Distinct patterns of restricted diffusion seen with various disease conditions can play an important diagnostic role. The association of certain diseases with a given restricted-diffusion pattern allows for a focused assessment to determine a specific etiology.

The pathophysiologic basis of restricted diffusion in the vast majority of cases results from failure of energy-dependent adenosine triphosphate production in cell membranes resulting in intracellular cytotoxic edema, usually implying cell death. Other less common mechanisms also occur, as seen with pyogenic abscess, where restricted diffusion derives from high viscosity and cellularity of pus. Restricted diffusion is the hallmark imaging feature of acute cerebral infarction and its most widely appreciated association, usually developing within 1 hour of insult. Less frequently this MRI abnormality is seen with other conditions including neoplasms, intracranial infections, traumatic brain injury, and demyelinating processes.¹ Unfamiliarity with nonstroke conditions that may manifest with restricted diffusion on MRI can pose a diagnostic challenge to the clinician. We review the causes of restricted diffusion in the context of distinct MRI patterns and outline a diagnostic approach.

Case vignettes and pattern types

The following are representative cases with diffusion-weighted images (DWI) showing the various patterns of restricted diffusion associated with acute and chronic disease conditions.

Case 1 A 75-year-old man developed sudden left-sided weakness and his electrocardiogram demonstrated atrial fibrillation. Examination showed hemiparesis on his left side with gaze deviation to the right. IV tissue plasminogen activator was administered. MRI demonstrated acute middle cerebral artery territory infarction (figure 1, A and B).

Case 2 An 87-year-old woman presented with a 2-month history of progressive left hemiparesis. EEG showed slowing on the left. Over the next 2 weeks, she developed cognitive decline

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Figure 1 Diffusion-weighted and apparent diffusion coefficient images for case studies

(A, B) Diffusion-weighted imaging (DWI) (arrowheads) and apparent diffusion coefficient (ADC) with restricted diffusion in right middle cerebral artery territory due to acute cerebral infarction. (C, D) DWI (arrowheads) and ADC with restricted diffusion of left parietooccipital cortex due to Creutzfeldt-Jakob disease. (E, F) DWI and ADC with restricted diffusion of cerebral cortex (arrows), basal ganglia, and thalamus (arrowhead) secondary to hyperammonemic encephalopathy. (G, H) DWI (arrowhead) and ADC with restricted diffusion of both caudate nuclei due to ischemic infarction. (I, J) DWI (arrowheads) and ADC with restricted diffusion of centrum semiovale from carbon monoxide poisoning. (K, L) DWI (arrowheads) and ADC with restricted diffusion of white matter and basal ganglia from hypoxic-ischemic injury. (M-O) DWI, ADC, and DWI with restricted diffusion of hemispheric white matter (arrowheads) and cerebral cortex (arrowhead) due to hypoxic-ischemic injury. (P, Q) DWI (arrowhead) and ADC with restricted diffusion of right cerebellar hemisphere secondary to pyogenic abscess. (R, S) DWI (arrowhead) and ADC with ring pattern restricted diffusion of posterior right frontal white matter due to demyelinating disease.

and myoclonic jerks of the right upper extremity. The initial MRI was interpreted as “early infarction” and follow-up after 1 week was interpreted as “spreading gyral infarction” (figure 1, C and D). The patient died on hospital day 10 and the CSF protein 14-3-3 result was positive; Creutzfeldt-Jakob disease (CJD) was diagnosed. Permission for autopsy was declined.

Case 3 A 49-year-old man with alcoholic hepatitis presented with hematemesis requiring emergent esophagogastroduodenoscopy that revealed portal hypertensive gastropathy and bleeding esophageal varices that were ligated. He gradually became unresponsive over the next several days. Laboratory studies showed an ammonia level of 233 $\mu\text{M/L}$. MRI showed features of hyperammonemic encephalopathy (figure 1, E and F).

Case 4 An 83-year-old man with medication-controlled hypertension presented with a 2-week history of progressive gait difficulty. Neurologic findings were characterized by cogwheel rigidity in the upper extremities and a paucity of spontaneous movement of face and arms. Gait was slow with short steps on a narrow base and the patient fell back with perturbation. MRI showed acute infarction of both caudate nuclei (figure 1, G and H).

Case 5 A 7-year-old girl was found unresponsive along with several other family members at home. Carboxyhemoglobin on admission was 21.2%. She was unresponsive for 5 days with spontaneous movement noted on day 3. EEG showed diffuse high-amplitude delta activity. She progressively improved and by week 8 spoke fluently and walked without assistance. A mild spastic diplegia with bilaterally extensor plantar response persisted. MRI done on hospital day 2 showed findings of acute carbon monoxide poisoning (figure 1, I and J).

Awareness of the disease entities associated with specific patterns on restricted diffusion can be helpful in focusing the diagnostic workup when the etiology is uncertain.

Case 6 A 28-year-old heroin abuser was found unresponsive at home. On admission, he was intubated and was unresponsive to verbal commands but had reactive pupils and intact doll's-eye response. EEG showed marked slowing and urine toxicology was positive for opiates. MRI done on admission showed changes of hypoxic-ischemic encephalopathy (figure 1, K and L). The patient died on hospital day 20.

Case 7 A 15-year-old girl had cardiorespiratory arrest while playing baseball. Cardiopulmonary resuscitation was administered and she was cardioverted on site by paramedics. She remained comatose for several weeks, then gradually began to awaken, track objects, and follow simple commands. MRI done on hospital day 6 showed changes of hypoxic-ischemic encephalopathy (figure 1, M–O). At 6 months she could stand independently, ambulate, comprehend, and respond verbally. She was independent in activities of daily living but with some recent memory impairment.

Case 8 A 76-year-old woman with nonalcoholic cirrhosis presented after 3 days of dizziness, imbalance, and gait difficulty. CT showed a round hypodense mass lesion primarily involving the right cerebellar hemisphere. MRI was done on hospital day 2 (figure 1, P and Q). A pyogenic abscess was drained from the cerebellar lesion.

Case 9 A 44-year-old woman presented with a 4-month progressive neurologic illness characterized by headache, focal weakness, and seizures. CSF showed 5 oligoclonal bands. She died several weeks after admission due to pulmonary embolism discovered at postmortem examination. MRI was done on admission (figure 1, R and S). Neuropathology was diagnostic of Balo concentric sclerosis.

DISCUSSION

When seen in other than an acute stroke setting, the significance of restricted diffusion is frequently not appreciated, resulting in missed or delayed diagnosis. Further, the bilateral symmetric appearance that frequently accompanies this MRI abnormality,^{2,3} particularly with involvement of cortical and deep gray structures, can be deceptive.

The importance of pattern recognition with restricted diffusion is appreciated considering not all areas of restricted diffusion manifest signal change on other sequences, and multiple areas may be involved without corresponding signal abnormality. The former is illustrated by CJD where restricted diffusion may be the only imaging abnormality,^{4,5} and the latter by ethylene glycol poisoning where the only restricted-diffusion abnormality is seen in white matter, while deep gray nuclei manifest only T2-weighted changes.⁶ Awareness of the disease entities associated with specific patterns on restricted diffusion can be helpful in focusing the diagnostic workup when the etiology is uncertain. Additionally, there are prognostic implications as seen with hypoxic-ischemic insult and hypoglycemia,^{7,8} where a poorer outcome is associated with involvement of deep gray nuclei as seen in our case 6 vs case 7, where the former died and the latter survived and is living independently.

Previous reports have addressed aspects of restricted diffusion on MRI.^{1,3,9–11} We here review the spectrum of causes of restricted diffusion and correlate them with their MRI pattern to outline a diagnostic approach. Nine distinct patterns of restricted diffusion that

Figure 2 Diagnostic patterns on restricted diffusion

*Subacute/chronic. B = basal ganglia; CJD = Creutzfeldt-Jakob disease; CO = carbon monoxide; HSE = herpes simplex encephalitis; H-I = hypoxic-ischemic; PRES = posterior reversible encephalopathy syndrome; RCVS = reversible cerebral vasoconstrictive syndrome; T = thalamus.

Table 1 Disease entities manifesting restricted diffusion^a

Hypoxic-ischemic (2–7) ^{8,11,e15}	Creutzfeldt-Jakob disease (2–4)^{4,5,10b}
Carbon monoxide poisoning (3–7) ^{e2,e3}	Herpes simplex encephalitis (2) ¹¹
Cyanide poisoning (4) ^{e11}	Other viral encephalitides (2, 4, 5) ^{11,e7,e8}
Ethylene glycol (2, 5) ⁶	Osmotic myelinolysis (4) ¹¹
Heroin (5) ^{e14}	Wernicke encephalopathy (4, 5) ^{e4}
Methanol poisoning (4, 6) ^{e12}	Chemotherapy (5) ^{16b}
Hypoglycemia (2–5, 7) ^{7,12,14,15}	Intravascular lymphomatosis (2) ^{e13b}
Hyperammonemia (2–4) ^{18,19}	Radiation therapy (5, 8) ^{17b}
Hyperglycemia (4) ^{11,13 b}	Metachromatic leukodystrophy (5) ^{e6b}
Arterial infarction (1, 4, 9, 11)	Head injury (8) ^{1b}
Venous infarction (1, 4, 11)	Neoplasm (8, 9) ^{1b}
Mitochondrial disease (2) ^{10,11b}	Demyelinating disease (8, 9) ^{1b}
Seizure (2–4, 7) ^{20,e1}	Abscess fungal, pyogenic, parasitic (8, 9) ^{e9,e10b}
Phenylketonuria (5) ^{e5b}	RCVS/PRES (5, 8) ^{e16,e17}
Abbreviations: PRES = posterior reversible encephalopathy syndrome; RCVS = reversible cerebral vasoconstrictive syndrome.	
^a Pattern type is presented in parentheses. e-References are available at neurology.org/cp .	
^b Subacute/chronic.	

include vascular territory, cortex, cortex–deep gray, deep gray, white matter/diffuse, deep gray–white matter, cortex–white matter, white matter/focal, and ring are described (figures 1 and 2). Accompanying DWI and corresponding apparent diffusion coefficient changes of the cases presented illustrate the various restricted-diffusion patterns.

Despite the wide range of conditions (table 1 and figure 2), a focused approach that includes laboratory investigation, CSF analysis, and select brain and cardiac studies can expeditiously screen for a specific etiology. Fundamental to the diagnostic evaluation is to

Supplemental Data

neurology.org/cp**Table 2** Diagnostic approach to restrictive diffusion on MRI

Clinical setting	Workup ^a
Onset of event: acute or chronic, static or progressive, history of drug abuse, toxic exposure, anoxia	Laboratory studies: routine metabolic panel to include: glucose, blood urea nitrogen, electrolytes, ammonia, blood and urine toxicology screen (heroin, cyanide, carboxyhemoglobin, methanol, ethanol, ethylene glycol), HIV and toxoplasmosis serology, liver function tests, and blood gases
Risk factors	CSF: routine studies, herpes simplex virus PCR, oligoclonal bands, protein 14-3-3, tau protein, viral panel (including West Nile and H1N1), JC virus PCR
Immunosuppression	Studies: EEG, echocardiogram, EKG
Insulin use	Other imaging: magnetic resonance venography, CT angiography
Radiation therapy	Molecular genetic and enzyme defect testing
Alcohol/liver disease	Brain biopsy
HIV infection	
Seizure	
Drug abuse/toxic exposure (CO, cyanide, methanol, heroin, chemotherapy, ethanol, ethylene glycol)	

^aFollowing CT and MRI.

determine if the condition is acute or chronic and whether the process is progressive or static. Considering the clinical setting and risk factors, if an acute process is suspected, a rapid diagnostic evaluation can be carried out (table 2). Excluding stroke, toxic-metabolic and hypoxic-ischemic events account for the majority of cases, while seizure and encephalitis are less frequent. If no etiology is determined from the initial assessment, more chronic conditions such as CJD and those associated with focal white matter and ring lesions as seen with MRI patterns 8 and 9 are considered. In the latter group, consideration of brain biopsy for diagnosis and treatment of certain infectious and neoplastic conditions is paramount. Infections include fungal and pyogenic abscess, toxoplasmosis, viral encephalitis including West Nile, N1H1, and herpes simplex encephalitis, progressive multifocal leukoencephalopathy, and prion-related CJD.^{10,e7-10} Additional historical and clinical factors will determine if further specialized blood tests and other investigations such as cerebral angiography are warranted to diagnose other potentially treatable chronic conditions (table 1).

Despite involvement of cortex and deep gray, white matter and cortex, or white matter and deep gray, simultaneous involvement of all 3 areas with restricted diffusion has not been observed. One can speculate that involvement of any 2 of these areas somehow exerts a protective effect on the third. A useful strategy in differentiating restrictive diffusion due to stroke vs seizure is to repeat the imaging study as DWI changes with seizure typically resolve when the seizures are controlled and persist with stroke. Also the pattern of involvement is different for the 2 conditions.

Although no pattern is pathognomonic, some are more specific than others, as seen with CJD, where isolated cortical involvement in a chronic setting is almost diagnostic.^{4,5,10} When the image pattern along with the clinical setting and risk factor profile are considered, the suggested diagnostic evaluation can be instrumental in identifying the cause of restricted diffusion. Familiarity with the specific diseases that can be associated with a given pattern of restricted diffusion can facilitate an otherwise challenging diagnosis.

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DISCLOSURES

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