Cytotoxic Lesions of the Corpus Callosum That Show Restricted Diffusion: Mechanisms, Causes, and Manifestations[1]

Jay Starkey, MD
Nobuo Kobayashi, MD
Yuji Numaguchi, MD, PhD
Toshio Moritani, MD, PhD

[1]From the Department of Radiology, St Luke's International Hospital, 9-1 Akashicho, Chuo, Tokyo 104-8560, Japan (J.S., N.K., Y.N.); and the Department of Radiology, University of Iowa Hospitals and Clinics, Iowa City, Iowa (T.M.). Recipient of a Magna Cum Laude award for an education exhibit at the 2015 RSNA Annual Meeting. Received April 3, 2016; revision requested September 1 and received September 22; accepted November 1. For this journal-based SA-CME activity, the authors, editor, and reviewers have disclosed no relevant relationships. **Address correspondence to** J.S. (e-mail: *jaystarkey@gmail.com*).

SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

■ Describe the imaging appearance of CLOCCs.

■ Discuss the likely mechanisms for the development of cytotoxic edema.

■ List the entities associated with CLOCCs.

See www.rsna.org/education/search/RG.

An earlier incorrect version of this article appeared online. This article was corrected on February 13, 2017.

Cytotoxic lesions of the corpus callosum (CLOCCs) are secondary lesions associated with various entities. CLOCCs have been found in association with drug therapy, malignancy, infection, subarachnoid hemorrhage, metabolic disorders, trauma, and other entities. In all of these conditions, cell-cytokine interactions lead to markedly increased levels of cytokines and extracellular glutamate. Ultimately, this cascade can lead to dysfunction of the callosal neurons and microglia. Cytotoxic edema develops as water becomes trapped in these cells. On diffusion-weighted magnetic resonance (MR) images, CLOCCs manifest as areas of low diffusion. CLOCCs lack enhancement on contrast material–enhanced images, tend to be midline, and are relatively symmetric. The involvement of the corpus callosum typically shows one of three patterns: *(a)* a small round or oval lesion located in the center of the splenium, *(b)* a lesion centered in the splenium but extending through the callosal fibers laterally into the adjacent white matter, or *(c)* a lesion centered posteriorly but extending into the anterior corpus callosum. CLOCCs are frequently but not invariably reversible. Their pathologic mechanisms are discussed, the typical MR imaging findings are described, and typical cases of CLOCCs are presented. Although CLOCCs are nonspecific with regard to the underlying cause, additional imaging findings and the clinical findings can aid in making a specific diagnosis. Radiologists should be familiar with the imaging appearance of CLOCCs to avoid a misdiagnosis of ischemia. When CLOCCs are found, the underlying cause of the lesion should be sought and addressed.

©RSNA, 2017 • radiographics.rsna.org

Introduction

Cytotoxic lesions of the corpus callosum (CLOCCs) are associated with many entities. It is important to recognize these lesions for what they are—secondary lesions. It is also important to be familiar with their known causes so that the source can be found and addressed and so that a misdiagnosis of ischemia can be avoided.

Cytokines, Glutamate, and Lesions of the Corpus Callosum

Cell-Cytokine Relationships

Complex interdependent mechanisms regulate cytokine levels and, ultimately, glutamate levels in the brain (1,2). With trauma, infection, and inflammation, macrophages become active and release the inflammatory cytokines interleukin 1 (IL-1) and IL-6, beginning the cascade that leads to cytokinopathy. Monocytes then activate and also release IL-1 and IL-6. T cells are subsequently recruited and

RadioGraphics

TEACHING POINTS

- Cytotoxic lesions of the corpus callosum (CLOCCs) are associated with many entities. It is important to recognize these lesions for what they are—secondary lesions.

- The net result of this cytokinopathy is massively increased amounts of glutamate in the extracellular space at levels 100 times the normal level or more.

- It is generally agreed that these callosal lesions with reduced diffusion (low apparent diffusion coefficient [ADC] value) are caused by cytotoxic edema. Therefore, we term these lesions *cytotoxic lesions of the corpus callosum* (CLOCCs).

- The involvement of the corpus callosum typically shows one of three patterns: *(a)* a small round or oval lesion located in the center of the splenium, *(b)* a lesion centered in the splenium but extending through the callosal fibers laterally into the adjacent white matter, or *(c)* a lesion centered posteriorly but extending into the anterior portion of the corpus callosum.

- CLOCCs are associated with drug therapy, malignancy, infections, subarachnoid hemorrhage (SAH), metabolic abnormalities, trauma, and other entities.

affect the endothelial cells, making the endothelial cells leaky (breaking down the blood-brain barrier) and stimulating them to produce tumor necrosis factor-α (TNF-α) (3–5). Astrocytes, in turn, are stimulated by IL-1 to release glutamate and block reuptake of glutamate, thus increasing extracellular glutamate (6). Microglia, which are the macrophages of the central nervous system (CNS), subsequently become activated and produce more cytokines and may initiate demyelination (5–7). Many of these cell-cytokine relationships include feedback loops that are exponentially amplified (7). The net result of this cytokinopathy is massively increased amounts of glutamate in the extracellular space at levels 100 times the normal level or more (Fig 1) (3,6,8).

Cytotoxic Edema
The excitotoxic action of glutamate on *N*-methyl-D-aspartate receptors, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors, sodium-potassium pumps, and aquaporins results in an influx of water into both astrocytes and neurons (3,8). This water is trapped within the cells, which results in intracellular edema and reduced diffusion, a condition termed *cytotoxic edema* (Fig 2).

Vulnerable Region
The corpus callosum and particularly the splenium are vulnerable to cytokinopathy. Compared with those in other brain areas, the neurons, astrocytes, and oligodendrocytes of the corpus callosum have a higher density of receptors, including cytokine receptors, glutamate and other excitatory amino acid receptors, toxin receptors, and drug receptors (9–11). This higher density leads to a ten-

dency for cytotoxic edema of the corpus callosum to develop when cytokinopathy occurs (12–14).

What to Call These Lesions
Secondary lesions of the corpus callosum have been called by many names, including "mild encephalopathy with reversible splenial lesions (MERS)," "reversible splenial lesion syndrome (RESLES)," "reversible splenial lesions" or "transient splenial lesions," "clinically silent lesions in the splenium of the corpus callosum," and "transient focal lesions in the splenium of the corpus callosum" (13,15–26). Much like the posterior reversible encephalopathy syndrome, the existing names for these callosal lesions are problematic for multiple reasons: *(a)* encephalopathy is not always mild (can be absent or severe) (24,27,28), *(b)* the lesions are not always completely reversible (27,28), and *(c)* the lesions are not always strictly splenial (27,29,30). In addition, the acronym MERS is easily confused with the acronym for Middle Eastern respiratory syndrome.

On the other hand, it is generally agreed that these callosal lesions with reduced diffusion (low apparent diffusion coefficient [ADC] value) are caused by cytotoxic edema (12–14,27,29,31). Therefore, we term these lesions *cytotoxic lesions of the corpus callosum* (CLOCCs).

Patterns of CLOCCs
Compared with the signal intensity of the adjacent parenchyma, CLOCCs demonstrate increased signal intensity on fluid-attenuated inversion-recovery (FLAIR) magnetic resonance (MR) images and show decreased signal intensity on T1-weighted MR images. Diffusion is reduced (mean ADC value, 0.31×10^{-3} mm^2/sec; range, 0.13×10^{-3} mm^2/sec to 0.48×10^{-3} mm^2/sec) (20). CLOCCs lack enhancement on contrast material–enhanced images, tend to be midline, and are relatively symmetric. The involvement of the corpus callosum typically shows one of three patterns: *(a)* a small round or oval lesion located in the center of the splenium, *(b)* a lesion centered in the splenium but extending through the callosal fibers laterally into the adjacent white matter, or *(c)* a lesion centered posteriorly but extending into the anterior portion of the corpus callosum (Fig 3).

Associated Entities
CLOCCs are associated with drug therapy, malignancy, infections, subarachnoid hemorrhage (SAH), metabolic abnormalities, trauma, and other entities (Table).

Drug-associated CLOCCs
CLOCCs were initially described in patients with seizures (13,32–39), and a number of cytokine

Figure 1. Drawing shows the cells and cytokines that are important in the development of CLOCCs. Cell-cytokine interactions lead to massively elevated extracellular glutamate levels.
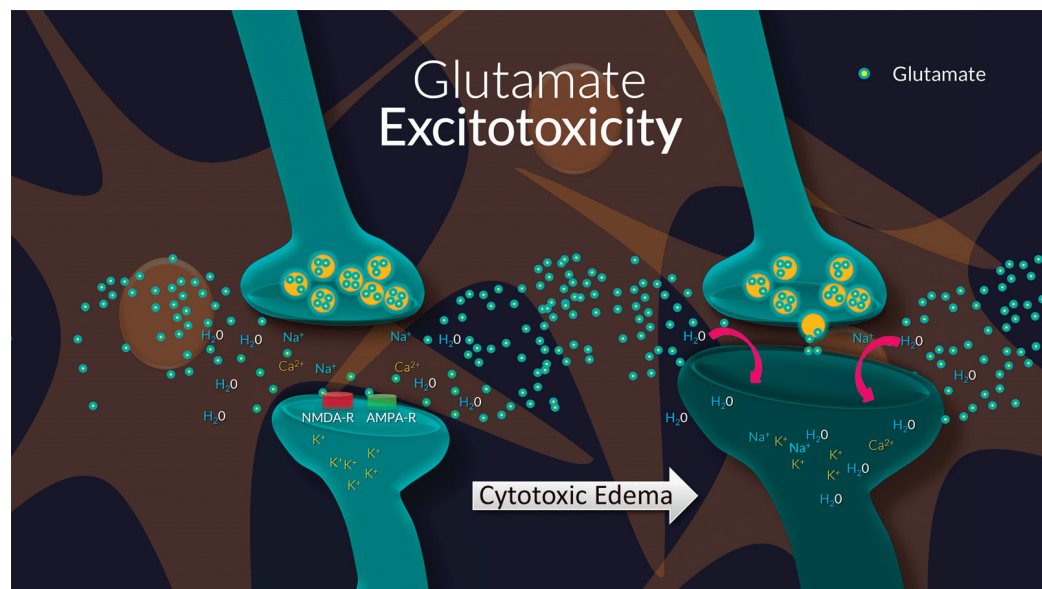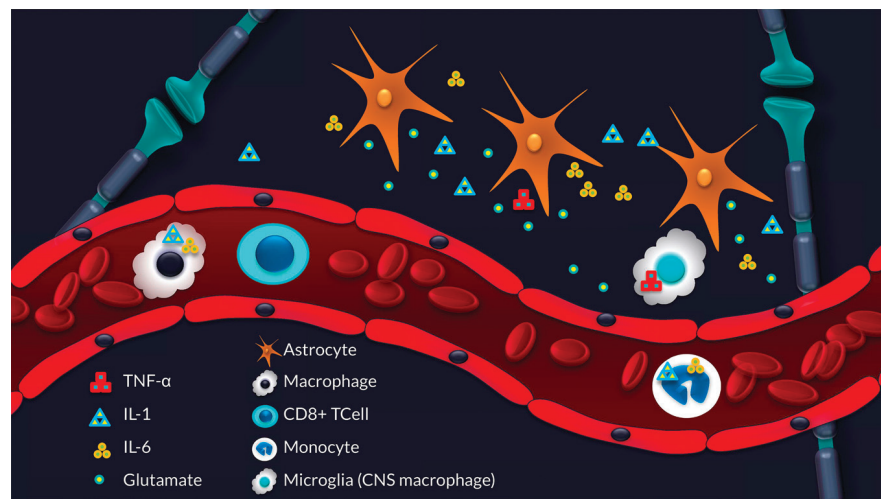
Figure 2. Drawing shows glutamate excitotoxicity. The extracellular glutamate binds with *N*-methyl-D-aspartate receptors *(NMDA-R)* and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors *(AMPA-R)*, allowing sodium ions *(Na⁺)* and calcium ions *(Ca⁺)* to enter cells, potassium ions *(K⁺)* to leave cells, and water *(H_2O)* to enter (pink arrows) and become trapped within neurons. This process leads to cytotoxic edema. Because the intracellular water cannot freely move, cytotoxic edema is manifest as reduced diffusion at MR imaging.

abnormalities have been reported in patients with seizures. For example, cytokine levels are different in patients with well-controlled seizures and those with poorly controlled seizures (32,40). However, the cytotoxic edema in patients with seizures is likely due only in part to the effect of the seizures, because therapy with antiseizure drugs itself can cause CLOCCs, even in patients without a history of seizures (Fig 4) (13,36). Therapy with antiseizure drugs such as carbamazepine can influence fluid balance systems (arginine vasopressin) and influence proinflammatory and proconvulsive cytokines. CLOCCs often develop after withdrawal of therapy with antiseizure drugs.

Since the discovery of the association of antiseizure drug therapy with CLOCCs, other types of drug therapy have been implicated—from chemotherapy to steroid therapy (23,41). In most instances, the findings from the clinical history alone are enough to allow recognition of when CLOCCs are drug associated, findings such as a history of seizures treated with antiseizure drugs or current chemotherapy. However, therapy with some drugs is associated with concurrent MR imaging findings that allow specific diagnosis. One such drug is metronidazole (42,43); in addition to the callosal lesion, accompanying lesions of the dentate nuclei are characteristic (Fig 5). Although the exact mechanism of the action of
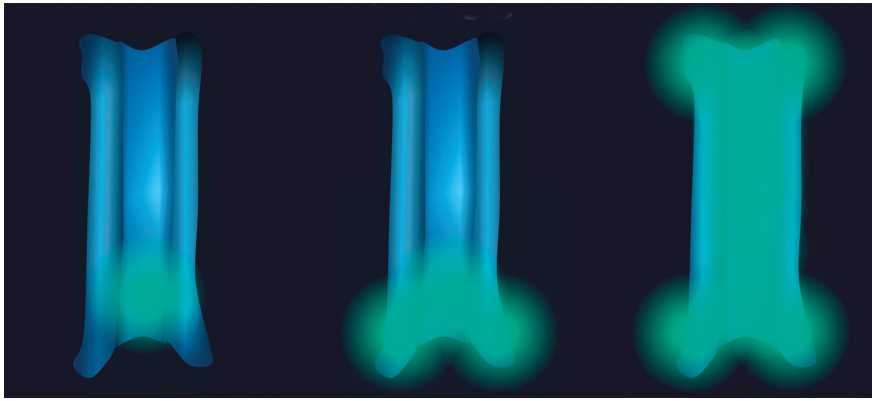
Figure 3. Drawing shows the three patterns of CLOCCs. Left: In the most common pattern, a small round or oval lesion is located in the center of the splenium. Center: In the second pattern, a lesion extends from the splenium through the callosal fibers laterally. Right: In the third pattern, a lesion extends into the anterior corpus callosum.
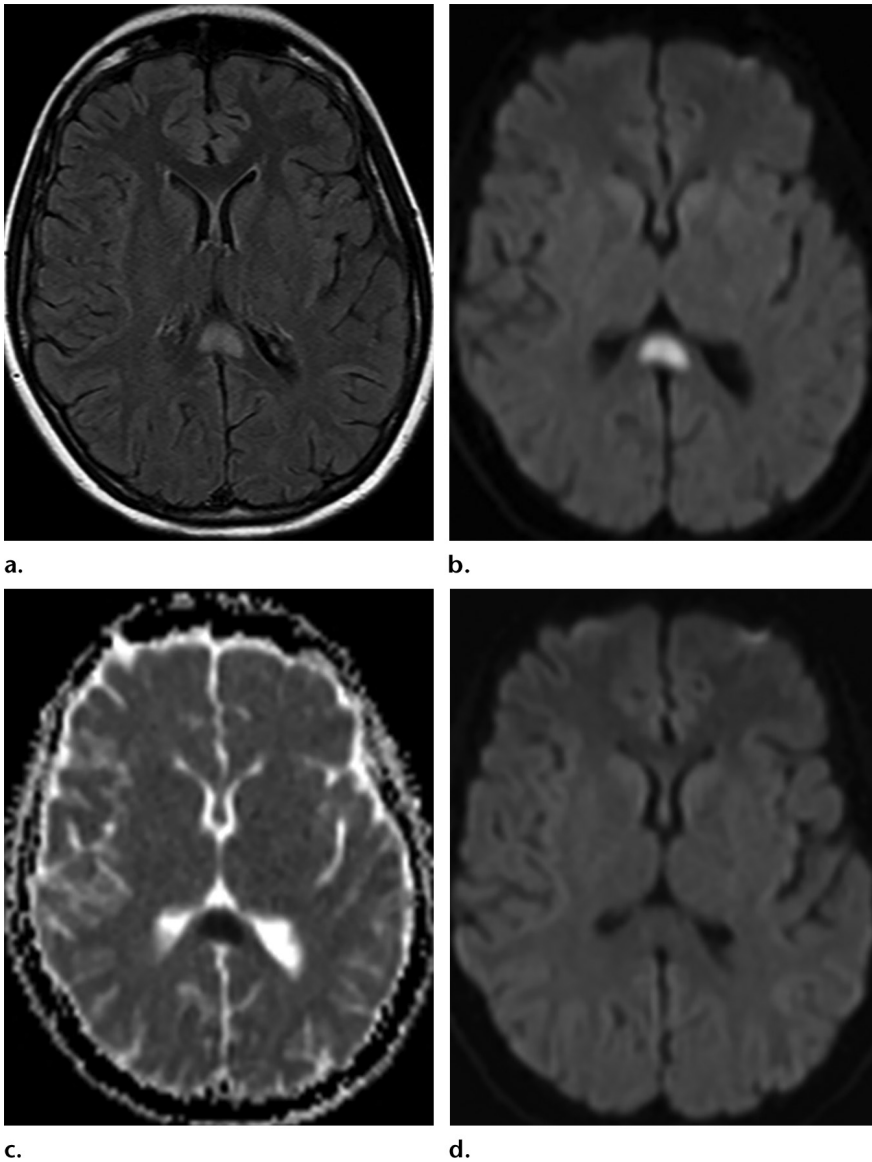

a.

b.

c.

d.

Figure 4. Drug-associated CLOCC in a 19-year-old woman with bipolar disorder treated with carbamazepine therapy who had no history of seizures. **(a–c)** Axial FLAIR MR image **(a)**, diffusion-weighted MR image **(b)**, and ADC map **(c)** show an ovoid focal lesion in the splenium. The signal intensity of the lesion is mildly increased on **a**. Diffusion is reduced. Contrast enhancement was absent (not shown). **(d)** Axial diffusion-weighted MR image obtained at the 1-month follow-up shows that the lesion had resolved completely.

RadioGraphics

Entities Associated with CLOCCs and Helpful Imaging and Clinical Features

Type of CLOCC	Helpful Imaging Features	Helpful Clinical Features	Reported Causes
Drug-associated CLOCCs	Abnormality of the dentate nuclei with metronidazole therapy	History of seizure, antiseizure therapy (eg, carbamazepine), chemotherapy, or other recent drug therapy	Carbamazepine, cyclosporine, diet pills with a sympathomimetic stimulant, fluorouracil, glufosinate ammonium, intravenous immunoglobulin therapy, lamotrigine, methyl bromide, metronidazole, neuroleptic malignant syndrome (amitriptyline, clozapine), phenytoin, corticosteroids, withdrawal of antiseizure therapy
Malignancy-associated CLOCCs	Evidence of CNS malignancy, including mass lesions and leptomeningeal enhancement	History of malignancy or chemotherapy	Acute lymphocytic leukemia, esophageal cancer, leptomeningeal glioblastomatosis, spinal meningeal melanocytoma
Infection-associated CLOCCs	Abscess formation or leptomeningeal enhancement, imaging findings that vary widely with the infectious agent and localization	Fever, leukocytosis, nuchal rigidity, altered mental status, history of travel to endemic areas (malaria)	Adenovirus, aseptic meningitis or encephalitis, Epstein-Barr virus (EBV), *Escherichia coli*, herpes, influenza virus A (H1N1), influenza, *Legionella*, malaria, measles, *Mycoplasma*, mumps, rotavirus, *Salmonella*, *Staphylococcus*, *Streptococcus*, tick-borne encephalitis, varicella-zoster virus
SAH-associated CLOCCs	Extensive hemorrhage within the subarachnoid space, lack of vessel irregularity on angiograms	Thunderclap headache, "worst headache of life," loss of consciousness, seizures in a patient with hypertension	Aneurysm, arteriovenous malformation
Metabolic disorder–associated CLOCCs	Classic central lesion in central pontine myelinolysis; symmetric lesions in the medial thalami and the mammillary bodies and surrounding the third ventricle and cerebral aqueduct in Wernicke encephalopathy; "eye of the panda" sign in Wilson disease	Fluid-electrolyte imbalances; history of cirrhosis or hepatic dysfunction, liver transplantation, malnutrition, or AIDS that may predispose to osmotic demyelination; history of alcoholism or malnutrition in Marchiafava-Bignami disease or Wernicke encephalopathy; Kayser-Fleischer rings in Wilson disease	Acute renal failure, alcoholism, extrapontine myelinolysis, central pontine myelinolysis, hepatic encephalopathy, hyperammonemia, hypernatremia, hypoglycemia, hyponatremia, malnutrition, Marchiafava-Bignami disease, Wernicke encephalopathy, Wilson disease
Trauma-associated CLOCCs	Brain contusions; multifocal punctate lesions on FLAIR, diffusion-weighted, or susceptibility-weighted MR images at the gray matter–white matter junction or in the corpus callosum or brainstem	Trauma with immediate loss of consciousness and persistent coma, altered mental status, or seizures	Trauma of various causes
CLOCCs associated with other entities	Varies with the cause	Varies with the cause	Acute high-altitude sickness, anti–glutamate receptor antibody, anti–voltage-gated potassium channel antibody, eclampsia, hemolytic uremic syndrome, vaccination, Kawasaki disease, posterior reversible encephalopathy syndrome, postpartum cerebral angiopathy, seizure without drug therapy, status epilepticus

a.
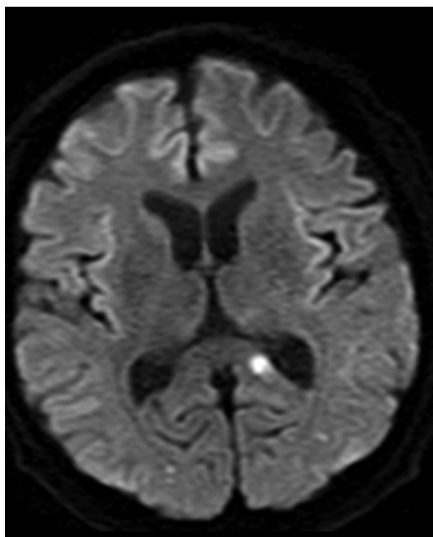
b.

c.

Figure 5. Drug-associated CLOCC in a 39-year-old man with lower extremity cellulitis treated with metronidazole who presented with new onset of altered mental status. **(a)** Axial FLAIR MR image at the level of the basal ganglia shows an ovoid focal lesion in the left lateral splenium. **(b)** Axial diffusion-weighted MR image shows reduced diffusion. **(c)** Axial FLAIR MR image at the level of the cerebellum shows characteristic hyperintensity of the dentate nuclei, without reduced diffusion (diffusion-weighted image not shown). Metronidazole therapy was discontinued, and the abnormality had resolved on the 10-day follow-up images (not shown).

metronidazole is unknown, the findings from animal models suggest that metronidazole causes a Wernicke-like encephalopathy that is due to cytotoxic edema (43).

Malignancy-associated CLOCCs
Occasionally, CLOCCs are seen in patients with malignancies (Fig 6) (20,27). Although CLOCCs can be seen in patients with other malignancies (probably caused by chemotherapy) (20,23), in those with CNS malignancies the CLOCCs can be found even before treatment (20), likely as a result of infiltration of meningeal cells with malignant cells, which results in a release of cytokines into the cerebrospinal fluid. Usually, patients will have a known primary malignancy at the time of diagnosis of CLOCCs. However, when CLOCCs are found in chemotherapy-naïve cancer patients, signs

of CNS dissemination such as leptomeningeal disease should be evaluated.

Infection-associated CLOCCs
Increased levels of cytokines are seen in the cerebrospinal fluid of patients with bacterial or viral meningoencephalitis (Fig 7) (2,4,6,7,44,45). Leukocytes produce proinflammatory cytokines and increase the permeability of the blood-brain barrier, allowing cytokines and inflammatory cells to enter the CNS. CNS cytokines activate glial cells (microglia, astrocytes, and oligodendrocytes), causing cytotoxic edema by way of excitotoxic mechanisms. Toxin-mediated immune activation also can cause endothelial injury and perivascular edema, as in patients with *Staphylococcus aureus* infection (Fig 8), *Legionella* infection, and hemolytic uremic syndrome. In patients with other infections, capillary blockage can induce ischemia,
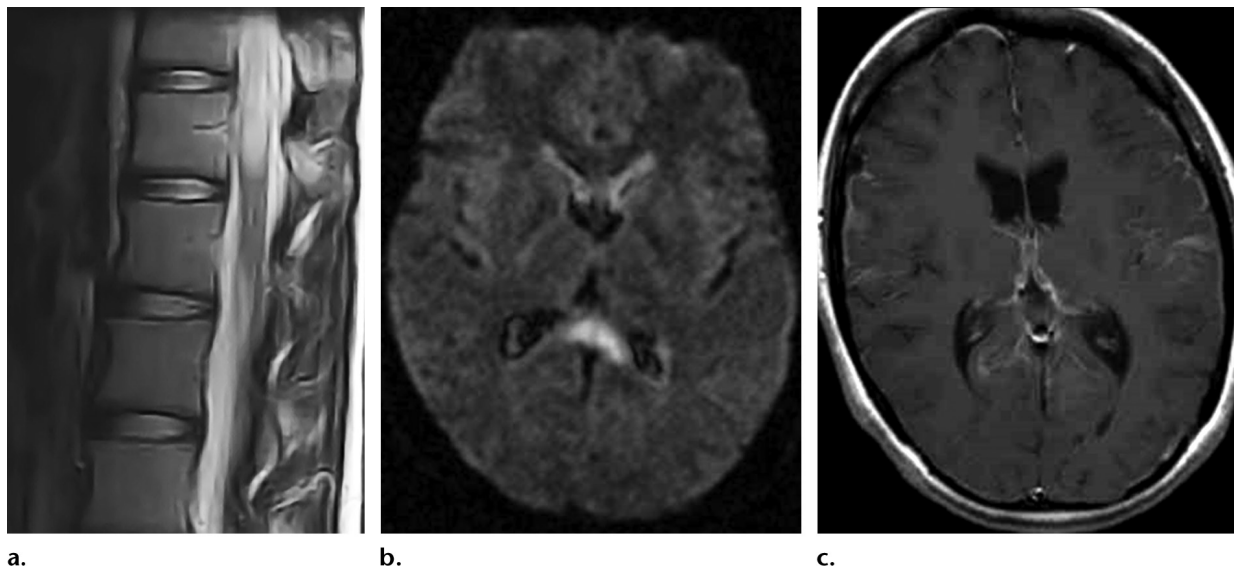
a.   b.   c.

Figure 6.   Malignancy-associated CLOCC in a 22-year-old woman presenting with paralysis and headache, in whom leptomeningeal glioblastomatosis was eventually diagnosed. **(a)** Sagittal T2-weighted MR image of the thoracolumbar spine shows a mass in the cord at the T11-T12 level. **(b)** Axial diffusion-weighted MR image shows an ovoid splenial lesion extending mildly off midline to the left and shows sparing of the surrounding callosal fibers. **(c)** Axial contrast-enhanced T1-weighted MR image shows a lack of lesion enhancement but diffuse leptomeningeal enhancement. The results of histopathologic examination of the biopsy specimen disclosed leptomeningeal glioblastomatosis from a glioblastoma multiforme in the spinal cord.

Figure 7. Infection-associated CLOCC in a 22-year-old man presenting with fever and headache, in whom mild aseptic encephalitis was diagnosed. **(a)** Axial diffusion-weighted MR image shows a typical ovoid lesion in the splenium. At the initial imaging examination 2 days earlier (images not shown), a FLAIR MR image had demonstrated normal findings, and a punctate focus of reduced diffusion had been depicted. **(b)** Axial diffusion-weighted MR image obtained at the 2-month follow-up shows that the lesion was nearly resolved. (Reprinted, with permission, from reference 45.)

a.   b.
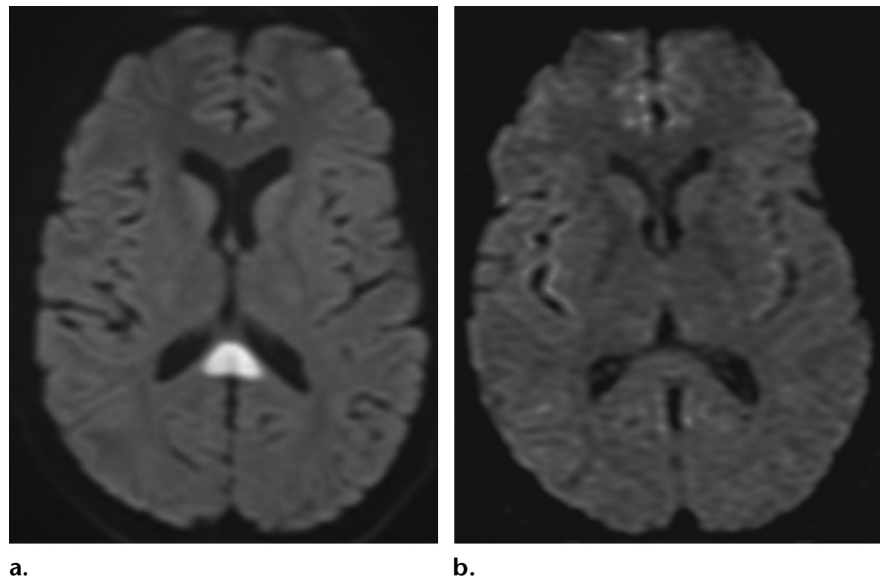
and cytokines can induce toxic effects in the cerebrum (46). In patients with malarial infection, CD8 T cells cause microvascular endothelial damage and leakage of proinflammatory cytokines (TNF-α, lymphotoxin-α, interferon-γ) (Fig 9) (44,45,47,48). Gastrointestinal infections such as infections with *E coli*, *Salmonella*, or rotavirus (Fig 10) may cause CLOCCs (49). Patients with EBV infection can develop CLOCCs (50), especially when the viral infection is accompanied by phagocytosis of erythrocytes, leukocytes, and platelets within the bone marrow by macrophages, a condition known as EBV-associated hemophagocytic lymphohistiocytosis (Fig 11) (51). Serum cytokine levels are markedly elevated in patients with EBV-associated hemophagocytic lymphohistiocytosis, which likely leads to the diffuse callosal involvement that can be present (Fig 12).

Infection-associated CLOCCs can be diagnosed in patients with signs of CNS infection, including fevers, leukocytosis, and nuchal rigidity. Patients with malarial infection will have a history of travel to endemic areas. Helpful accompanying imaging findings may include abscess formation, leptomeningeal enhancement, or hydrocephalus; in immunocompromised patients with angioinvasive fungal infections such as aspergillosis, an abscess with weak ring
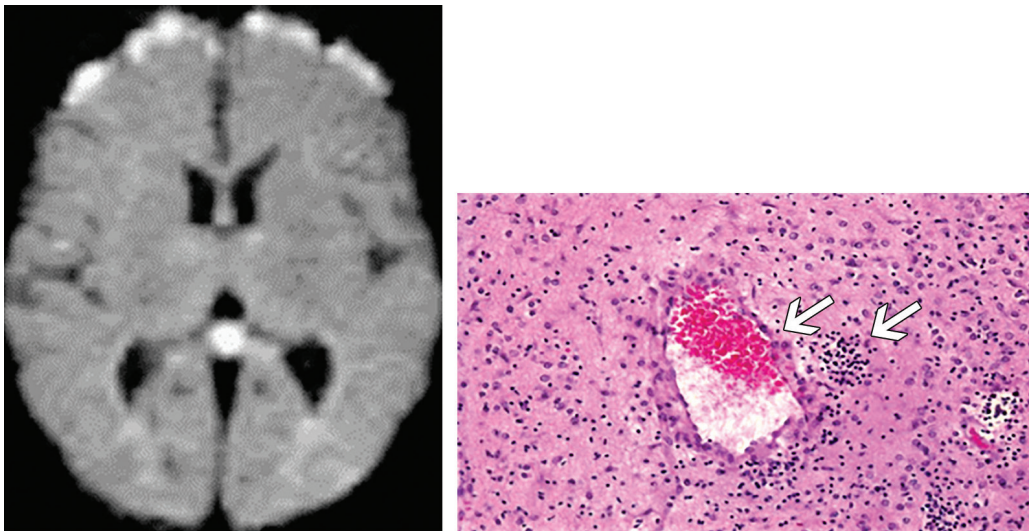
a.   **b.**

Figure 8. Infection-associated CLOCC in a 1-month-old male infant presenting with lethargy and high fever, in whom *S aureus* meningitis and vasculitis were diagnosed. **(a)** Axial diffusion-weighted MR image shows bilateral subdural collections with frontal subpial cortical infarctions and a focal splenial lesion. Contrast-enhanced images disclosed diffuse leptomeningeal enhancement (not shown). **(b)** High-power photomicrograph of a postmortem specimen shows perivascular inflammatory cell infiltration (arrows), with edema and vasculitis involving the walls of the small arteries. (Hematoxylin-eosin [H-E] stain; original magnification, ×200.)

enhancement, microhemorrhages, or areas of focal ischemia may be found (46).

SAH-associated CLOCCs

CLOCCs can be seen in patients with SAH. These callosal cytotoxic lesions should not be confused with vasospasm-related infarction. A lack of vessel irregularity at angiography is helpful in making the diagnosis. The amount of hemorrhage may be related to the development of CLOCCs, which is probably less likely to occur in patients with limited SAH, for example, from rupture of a middle cerebral artery aneurysm with the SAH limited to only the sylvian fissure. Development of CLOCCs is likely related to the irritating properties of blood products; in patients with SAH, markedly elevated levels of cytokines (IL-1β, IL-6, and TNF-α) are found in the cerebrospinal fluid, likely causing the cytotoxic edema (Fig 13) (52,53). In some studies, investigators have found a correlation between cytokine levels and an eventual need for shunting (54).

Metabolic Disorder–associated CLOCCs

Ammonia is likely the main culprit in hepatic encephalopathy (Fig 14) (55,56) and is associated at autopsy with cytotoxic changes in astrocytes and neurons (57). Acute toxic effects of ammonia cause a cytokine surge and increased glutamate with excessive activation of *N*-methyl-D-aspartate receptors (56,58–60). An additional imaging finding that may be suggestive of hepatic encephalopathy is high signal intensity in the globus pallidus on T1-weighted MR images (61).

Extrapontine myelinolysis may involve the splenium, basal ganglia, thalamus, or middle cerebellar peduncles (Fig 15) and is often associated with central pontine myelinolysis (Fig 16) (45,62–64). Diffusion-weighted MR imaging can be used to detect the lesions in the early phase as hyperintense lesions with decreased ADC, findings that represent cytotoxic edema.

The causes of extrapontine myelinolysis and central pontine myelinolysis seem to be multifactorial. Underlying conditions such as liver transplantation, alcohol abuse, malnutrition, AIDS, and hyponatremia increase the susceptibility to osmotic stress (Fig 17). Massive accumulations of microglia expressing proinflammatory cytokines (TNF-α, interferon-γ) have been observed in areas of osmotic demyelination (65).

Marchiafava-Bignami disease is a related condition in which abnormalities of the corpus callosum develop in patients with alcoholism and malnutrition. The callosal lesions have a predilection for the body of the corpus callosum but may occur in the splenium. They are often reversible with treatment (66).

Trauma-associated CLOCCs

Diffuse axonal injury is often associated with focal round or oval lesions in the corpus callosum (Fig 18) (14,27,67). These lesions are often
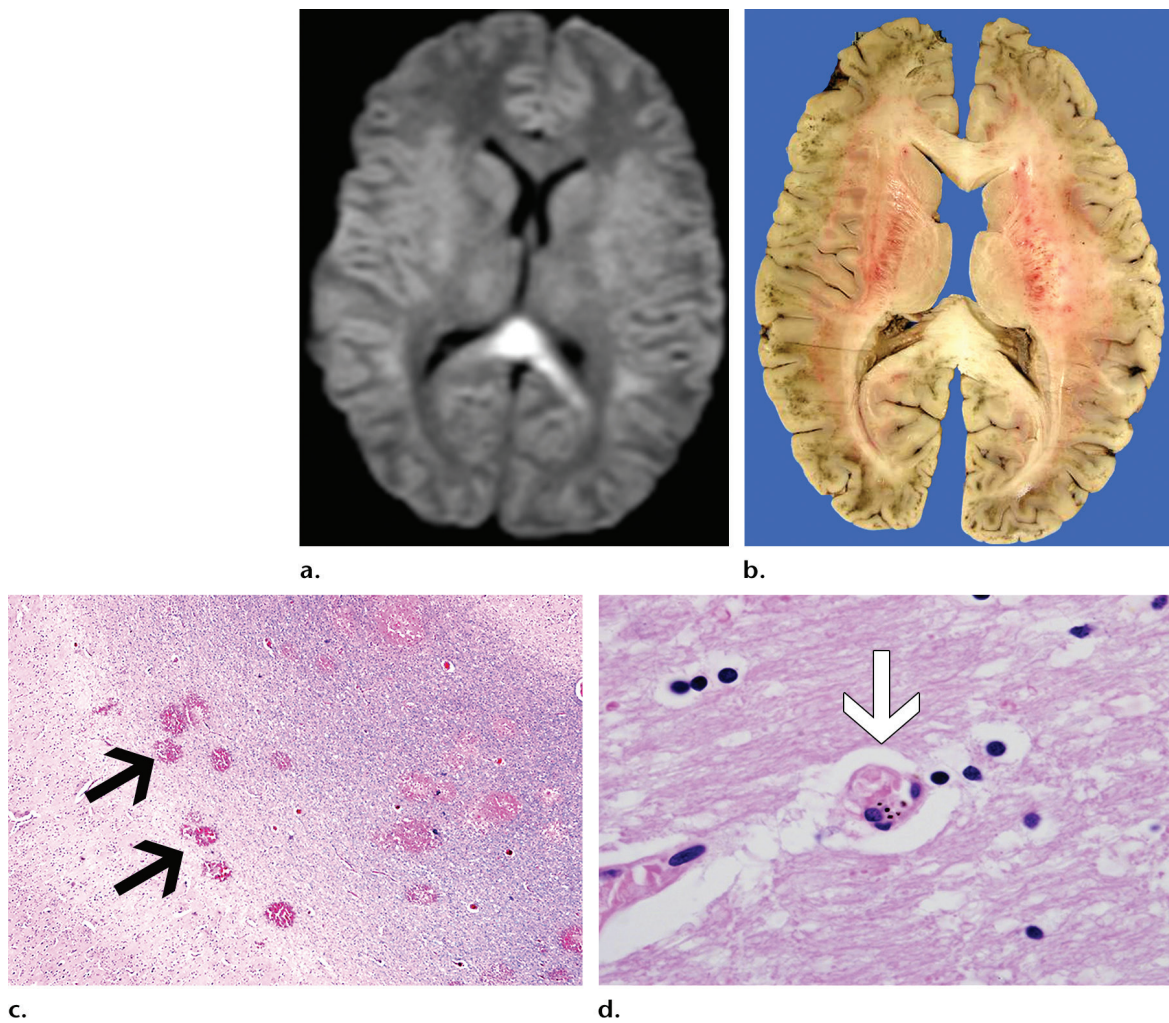
a.

b.

c.

d.

Figure 9. Infection-associated CLOCC in a 19-year-old woman presenting with headache, fever, and influenza-like symptoms after travel to Mozambique, in whom cerebral malaria was diagnosed. **(a)** Axial diffusion-weighted MR image shows a splenial lesion extending into the posterior deep white matter laterally. Diffuse microhemorrhages were seen in the subcortical white matter on susceptibility-weighted MR images (not shown). **(b)** Photograph of a cross-section of the gross specimen shows diffuse petechial hemorrhages. **(c)** High-power photomicrograph shows ring hemorrhages (arrows). (H-E stain; original magnification, ×100.) **(d)** High-power photomicrograph shows "Dürck granulomas" (arrow; areas of rarefied brain with activated microglia) and malarial deposits in red blood cells. (H-E stain; original magnification, ×400.) (Reprinted, with permission, from reference 45.)

Figure 10. Infection-associated CLOCC in a 5-year-old boy presenting with diarrhea and altered mental status, in whom rotavirus gastroenteritis was diagnosed. Axial diffusion-weighted MR image shows a splenial lesion extending into the posterior deep white matter laterally; the lesion extended into the body of the corpus callosum and the genu (better demonstrated on other images; not shown). The lesion had mostly resolved by day 4.
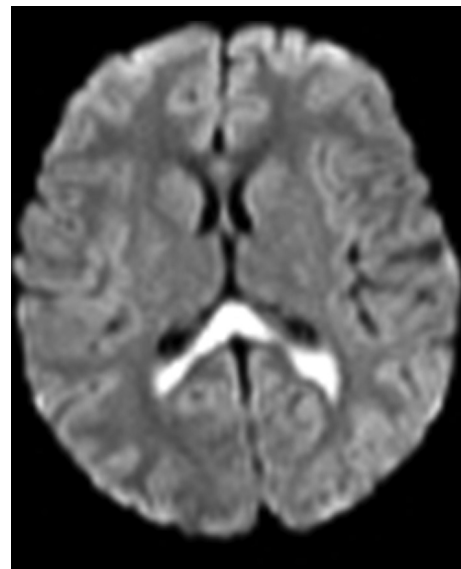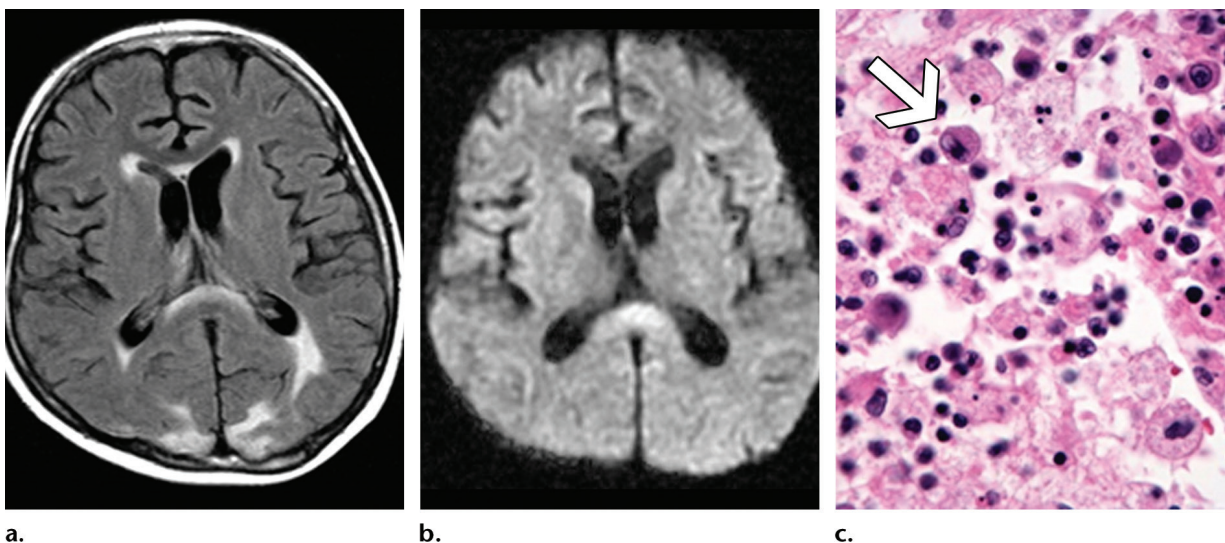
Figure 11. Infection-associated CLOCC in a 13-year-old boy presenting with altered mental status, hepatosplenomegaly, and hypercytokinemia, in whom EBV infection was diagnosed and treated with cyclosporine. **(a)** Axial FLAIR MR image shows a hyperintense oblong splenial lesion and mild involvement of the anterior corpus callosum. Occipital hyperintensity is also depicted, which is typical with cyclosporine therapy but atypical for CLOCCs. **(b)** Axial diffusion-weighted MR image shows reduced diffusion in the callosal lesions but not the occipital lesions. **(c)** High-power photomicrograph shows infiltration with hemophagocytic histiocytes (arrow) and atypical lymphocytes, findings consistent with EBV-associated hemophagocytic lymphohistiocytosis. The patient died despite treatment. (H-E stain; original magnification, ×400.) (Reprinted, with permission, from reference 76.)
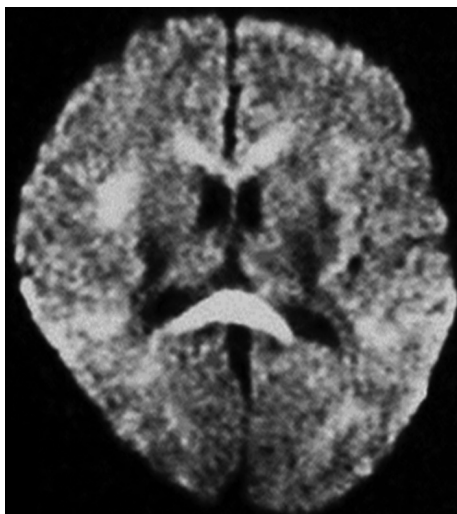

Figure 12. Infection-associated CLOCC in a 6-year-old girl presenting with fever, hepatic dysfunction, and histiocytosis with hemophagocytosis, who received a diagnosis of EBV-associated hemophagocytic lymphohistiocytosis. Axial diffusion-weighted MR image shows an abnormality involving the whole corpus callosum and extending into the hemispheric white matter. The patient died despite treatment with immunosuppressant therapy and plasma exchange. (Reprinted under a CC BY-NC-ND license from reference 77.)

located in the splenium but can involve the body of the corpus callosum or the genu (Fig 19). The callosal lesions may be symmetric or asymmetric, may be single or multiple, and may be associated with lesions of the fornices, internal capsules, superior cerebellar peduncles, midbrain, and white matter. Callosal lesions with symmetric involvement are often partially or fully reversible (14,27,67). In patients with diffuse axonal injury, reduced diffusion is present in the acute phase, representing cytotoxic edema. Dual mechanisms are presumed, primarily *(a)* leakage of glutamate caused by axonal disruption and *(b)* secondary release of cytokines and glutamate, which produce swelling in the surrounding myelin sheaths and astrocytes (5,14,67).

Additional findings in patients with diffuse axonal injury include punctate lesions at the gray matter–white matter junction, within the corpus callosum, or within the brainstem (68). Lesions are often hyperintense on FLAIR MR images, with reduced diffusion on diffusion-weighted MR images. Use of susceptibility-weighted pulse sequences may demonstrate microhemorrhages. Clinically, patients usually have loss of consciousness at the time of injury, with prolonged coma, altered mental status, or seizures. The prognosis is generally poor.

CLOCC Associations with Other Entities
CLOCCs have been associated with many other entities. In patients with acute high-altitude sickness (high-altitude cerebral edema), a history of a recent climb will be obvious. It should be noted that lesions have been described without reduced ADC (69); this finding is likely due to the timing of imaging, because ADC reduction in the splenium tends to occur in the acute stages of altitude sickness (31,70). CLOCCs

Figure 13. SAH-associated CLOCCs in three different patients presenting with acute-onset headache and altered mental status, in whom nontraumatic SAH without vasospasm was diagnosed. **(a)** Axial computed tomographic (CT) image of a 68-year-old man shows a representative initial CT image with a modified Fisher group 3 hemorrhage. **(b)** Axial diffusion-weighted MR image of the same man as in **a** shows a lesion in the posterior body to splenium of the corpus callosum. No cause for SAH was found. He required long-term shunting for hydrocephalus. **(c)** Axial diffusion-weighted MR image of a 42-year-old man shows a lesion in the posterior body to splenium of the corpus callosum. No cause for SAH was found. **(d)** Axial diffusion-weighted MR image of a 53-year-old man shows a lesion in the splenium of the corpus callosum. A dissecting vertebral artery aneurysm was found, and a coil was inserted. The patient required long-term shunting for hydrocephalus. He had mild atrophy in the area of the abnormality at the 1-year follow-up (not shown).
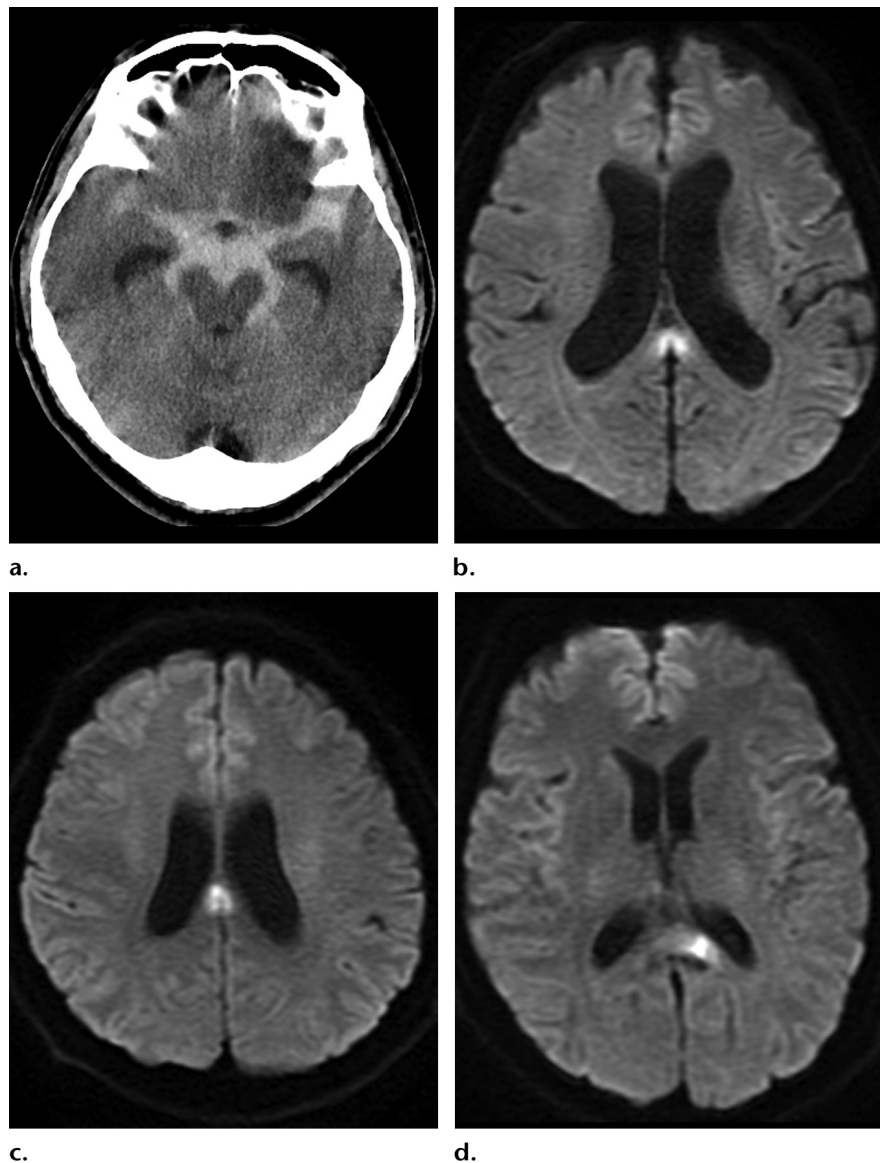
have been described in association with hypertension in patients with preeclampsia or eclampsia and patients with posterior reversible encephalopathy syndrome (71). As mentioned previously, seizures or status epilepticus can be associated with CLOCCs, even in patients who are not receiving therapy. Finally, numerous immune-related entities have been associated with CLOCCs, including anti–glutamate receptor antibodies (17), anti–voltage-gated potassium channel antibodies (72), hemolytic uremic syndrome (73), vaccination (25), Kawasaki disease (74), and postpartum cerebral angiopathy (75).

Differentiation from Primary Callosal Lesions

Occlusion of the distal branches of the anterior cerebral artery may result in ischemic infarction of the corpus callosum (27). Acute disseminated encephalomyelitis can also involve the corpus

callosum. Lesions in either of these conditions tend to be asymmetric. In addition, infarctions in the anterior cerebral artery territory tend to occur after surgery, such as after aneurysm clipping. Patients with multiple sclerosis often have typical periventricular white matter lesions. Finally, entities such as lymphoma or glioblastoma may involve the same regions but display a more aggressive appearance. MR angiographic images or contrast-enhanced MR images may help differentiate these lesions from CLOCCs when the imaging appearance is ambiguous.

Conclusion

CLOCCs are secondary lesions associated with drug therapy, malignancies, infections, SAH, metabolic disorders, trauma, and other entities. CLOCCs demonstrate reduced diffusion from cytotoxic edema. They are usually ovoid and located in the splenium but may be more exten-
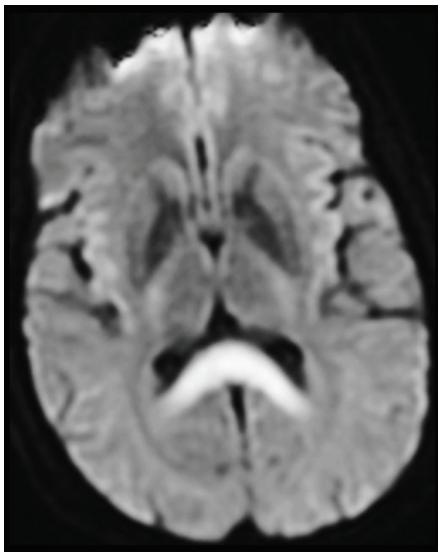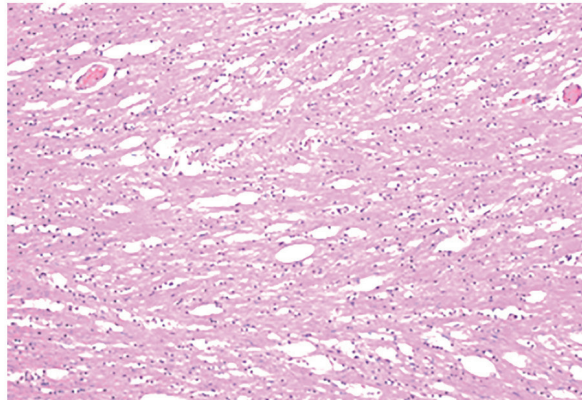
Figure 14.   Metabolic disorder–associated CLOCC in a 56-year-old man with liver cirrhosis caused by α_1-antitrypsin deficiency, who presented with new onset of confusion and in whom hepatic encephalopathy was diagnosed. **(a)** Axial diffusion-weighted MR image shows a lesion in the splenium extending into the deep white matter. The deep white matter also demonstrated mild, diffuse high T2 signal intensity without diffusion abnormality (not shown). **(b)** High-power photomicrograph of a specimen of the corpus callosum shows a lack of myelin with vacuolization. (Luxol fast blue stain; original magnification, ×200.)
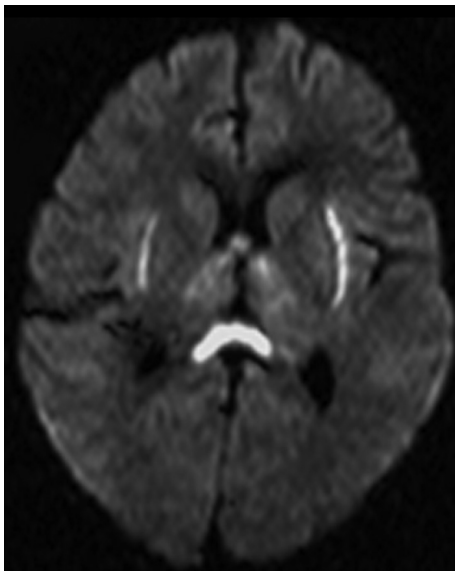

Figure 15.   Metabolic disorder–associated CLOCC in a 7-year-old boy presenting with loss of consciousness after rapid correction of hyponatremia, in whom extrapontine myelinolysis was diagnosed. Axial diffusion-weighted MR image shows an oblong lesion in the splenium. Lesions are also depicted in the external capsules, thalami, and fornices. A single lesion was also found in the deep white matter (not shown).

sive, with involvement of the body of the corpus callosum and the genu. CLOCCs are frequently but not invariably reversible. When they are present, their underlying cause should be sought and addressed.

References

1. Miller AH, Haroon E, Raison CL, Felger JC. Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. Depress Anxiety 2013;30(4):297–306.
2. Phelps C, Korneva E, eds. Neuroimmune biology. Vol 6, Cytokines and the brain. Amsterdam, the Netherlands: Elsevier, 2008.
3. Leonoudakis D, Braithwaite SP, Beattie MS, Beattie EC. TNFα-induced AMPA-receptor trafficking in CNS neurons: relevance to excitotoxicity? Neuron Glia Biol 2004;1(3): 263–273.
4. Kim YS, Honkaniemi J, Sharp FR, Täuber MG. Expression of proinflammatory cytokines tumor necrosis factor-α and interleukin-1β in the brain during experimental group B streptococcal meningitis. Brain Res Mol Brain Res 2004;128(1):95–102.
5. Kita T, Tanaka T, Tanaka N, Kinoshita Y. The role of tumor necrosis factor-α in diffuse axonal injury following fluid-percussive brain injury in rats. Int J Legal Med 2000;113 (4):221–228.
6. Prow NA, Irani DN. The inflammatory cytokine, interleukin-1 beta, mediates loss of astroglial glutamate transport and drives excitotoxic motor neuron injury in the spinal cord during acute viral encephalomyelitis. J Neurochem 2008;105(4): 1276–1286.
7. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. Microbiol Mol Biol Rev 2012;76(1):16–32.
8. Matute C, Alberdi E, Domercq M, et al. Excitotoxic damage to white matter. J Anat 2007;210(6):693–702.
9. Hassel B, Boldingh KA, Narvesen C, Iversen EG, Skrede KK. Glutamate transport, glutamine synthetase and phosphate-activated glutaminase in rat CNS white matter: a quantitative study. J Neurochem 2003;87(1):230–237.
10. Domercq M, Matute C. Expression of glutamate transporters in the adult bovine corpus callosum. Brain Res Mol Brain Res 1999;67(2):296–302.
11. Goursaud S, Kozlova EN, Maloteaux JM, Hermans E. Cultured astrocytes derived from corpus callosum or cortical grey matter show distinct glutamate handling properties. J Neurochem 2009;108(6):1442–1452.

Figure 16. Metabolic disorder–associated CLOCC in a 54-year-old man presenting with new onset of slurred speech and confusion after liver transplantation, in whom mixed central pontine myelinolysis and extrapontine myelinolysis were diagnosed. **(a)** Axial diffusion-weighted MR image at the level of the basal ganglia shows an ovoid lesion in the splenium. **(b)** Axial diffusion-weighted MR image at the level of the cerebellum shows reduced diffusion in the middle cerebellar peduncles. On FLAIR MR images (not shown), the pons demonstrated mild diffuse hyperintensity without corresponding reduced diffusion. Extrapontine myelinolysis has been reported to precede central pontine myelinolysis, as in this case (64). (Reprinted, with permission, from reference 45.)
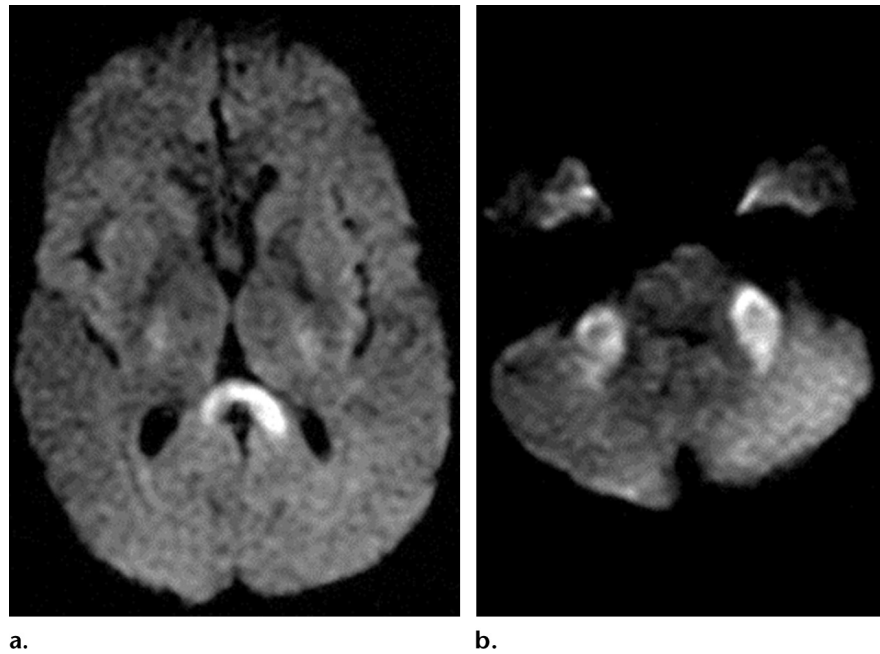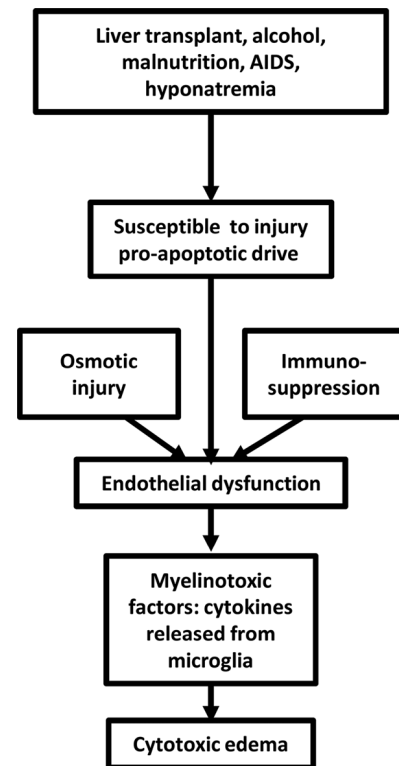

a.

b.

Figure 17. Flowchart depicts how cytotoxic edema develops in patients at risk for extrapontine myelinolysis and/or central pontine myelinolysis.

12. Moritani T, Smoker WR, Sato Y, Numaguchi Y, Westesson PL. Diffusion-weighted imaging of acute excitotoxic brain injury. AJNR Am J Neuroradiol 2005;26(2):216–228.
13. Prilipko O, Delavelle J, Lazeyras F, Seeck M. Reversible cytotoxic edema in the splenium of the corpus callosum related to antiepileptic treatment: report of two cases and literature review. Epilepsia 2005;46(10):1633–1636.
14. Takayama H, Kobayashi M, Sugishita M, Mihara B. Diffusion-weighted imaging demonstrates transient cytotoxic edema involving the corpus callosum in a patient with diffuse brain injury. Clin Neurol Neurosurg 2000;102(3):135–139.
15. Conti M, Salis A, Urigo C, Canalis L, Frau S, Canalis GC. Transient focal lesion in the splenium of the corpus callosum: MR imaging with an attempt to clinical-physiopathological explanation and review of the literature. Radiol Med (Torino) 2007;112(6):921–935.
16. Kim TY, Park DW, Park CK, Lee YJ, Lee SR. Reversible splenial lesion in the corpus callosum on MRI after ingestion of a herbicide containing glufosinate ammonium: a case report. J Korean Soc Radiol 2014;70(6):399–402. https://doi.org/10.3348/jksr.2014.70.6.399. Published online June 3, 2014.
17. Fujiki Y, Nakajima H, Ito T, Kitaoka H, Takahashi Y. A case of clinically mild encephalitis/encephalopathy with a reversible splenial lesion associated with anti-glutamate receptor antibody [in Japanese]. Rinsho Shinkeigaku 2011; 51(7):510–513.
18. Takanashi J, Barkovich AJ, Shiihara T, et al. Widening spectrum of a reversible splenial lesion with transiently reduced diffusion. AJNR Am J Neuroradiol 2006;27(4):836–838.
19. Bulakbasi N, Kocaoglu M, Tayfun C, Ucoz T. Transient splenial lesion of the corpus callosum in clinically mild influenza-associated encephalitis/encephalopathy. AJNR Am J Neuroradiol 2006;27(9):1983–1986.
20. Maeda M, Tsukahara H, Terada H, et al. Reversible splenial lesion with restricted diffusion in a wide spectrum of diseases and conditions. J Neuroradiol 2006;33(4):229–236.
21. Takanashi J, Barkovich AJ, Yamaguchi K, Kohno Y. Influenza-associated encephalitis/encephalopathy with a reversible lesion in the splenium of the corpus callosum: a case report and literature review. AJNR Am J Neuroradiol 2004;25(5):798–802.
22. Yokota S, Imagawa T, Miyamae T, et al. Hypothetical pathophysiology of acute encephalopathy and encephalitis related to influenza virus infection and hypothermia therapy. Pediatr Int 2000;42(2):197–203.
23. Tha KK, Terae S, Sugiura M, et al. Diffusion-weighted magnetic resonance imaging in early stage of 5-fluorouracil-induced leukoencephalopathy. Acta Neurol Scand 2002;106(6): 379–386.
24. Tada H, Takanashi J, Barkovich AJ, et al. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion. Neurology 2004;63(10):1854–1858.
25. Takanashi J, Shiihara T, Hasegawa T, et al. Clinically mild encephalitis with a reversible splenial lesion (MERS) after mumps vaccination. J Neurol Sci 2015;349(1-2):226–228.
26. Garcia-Monco JC, Cortina IE, Ferreira E, et al. Reversible splenial lesion syndrome (RESLES): what's in a name? J Neuroimaging 2011;21(2):e1–e14.
27. Park MK, Hwang SH, Jung S, Hong SS, Kwon SB. Lesions in the splenium of the corpus callosum: clinical and radiological implications. Neurol Asia 2014;19(1):79–88. http://www.neurology-asia.org/articles/neuroasia-2014-19(1)-079.pdf.
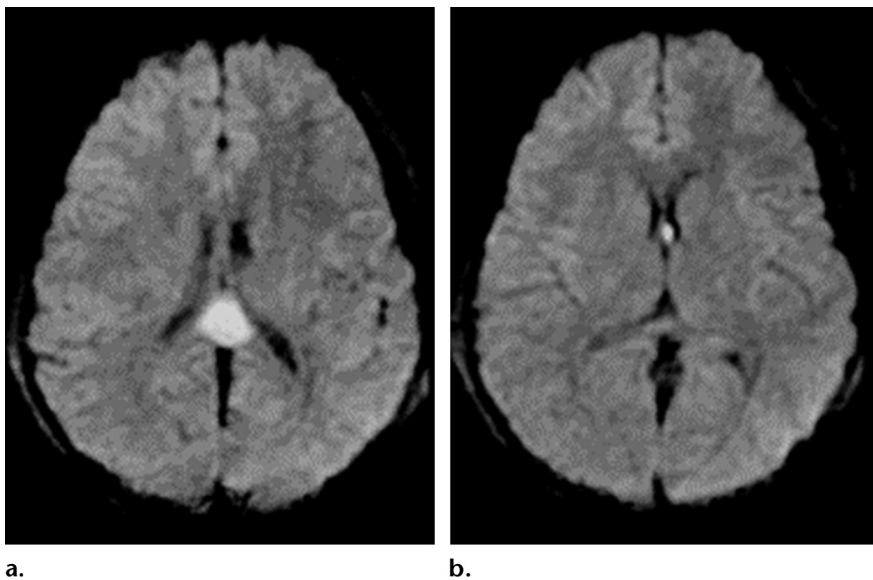
Figure 18. Trauma-associated CLOCC in an 11-year-old boy with poor results of a neurologic examination performed after head trauma, in whom diffuse axonal injury was diagnosed. **(a)** Axial diffusion-weighted MR image shows an ovoid lesion in the splenium extending into the body of the corpus callosum. **(b)** Axial diffusion-weighted MR image obtained at a slightly lower level than **a** shows additional areas of reduced diffusion in the fornices.
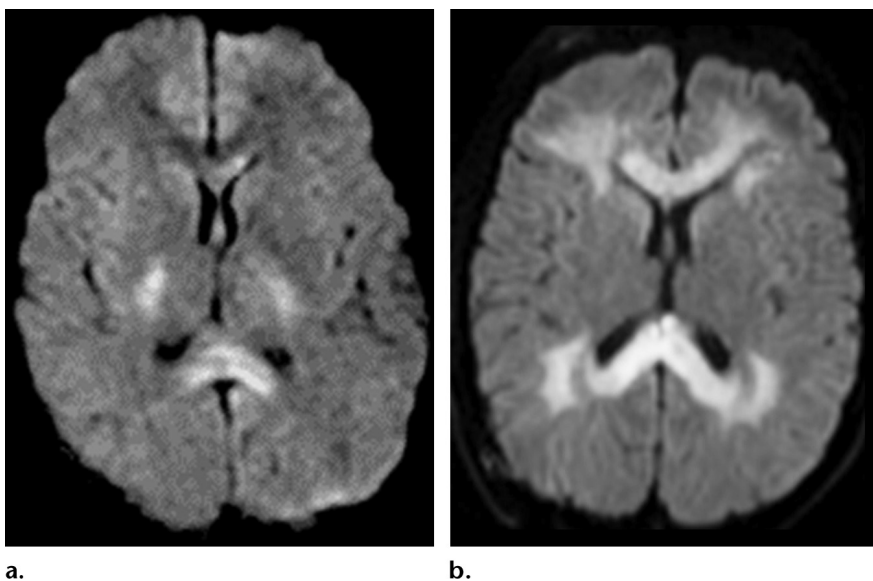

Figure 19. Trauma-associated CLOCCs in two different patients with diffuse axonal injury, in whom susceptibility-weighted MR images showed hemorrhagic foci (not shown). **(a)** Axial diffusion-weighted MR image of a 30-year-old man shows lesions in the splenium extending laterally and lesions bilaterally in the thalami and internal capsules, as well as the left genu. **(b)** Axial diffusion-weighted MR image of a 24-year-old man shows reduced diffusion involving the entire corpus callosum and extending into the adjacent deep white matter. In both cases, fractional anisotropy was preserved (not shown), a finding suggestive of pure cytotoxic edema and consistent with the dual pathogenesis thought to be present in diffuse axonal injury.

28. Doherty MJ, Jayadev S, Watson NF, Konchada RS, Hallam DK. Clinical implications of splenium magnetic resonance imaging signal changes. Arch Neurol 2005;62(3):433–437.
29. Kazi AZ, Joshi PC, Kelkar AB, Mahajan MS, Ghawate AS. MRI evaluation of pathologies affecting the corpus callosum: a pictorial essay. Indian J Radiol Imaging 2013;23(4):321–332.
30. Böttcher J, Kunze A, Kurrat C, et al. Localized reversible reduction of apparent diffusion coefficient in transient hypoglycemia-induced hemiparesis. Stroke 2005;36(3):e20–e22.
31. Kallenberg K, Bailey DM, Christ S, et al. Magnetic resonance imaging evidence of cytotoxic cerebral edema in acute mountain sickness. J Cereb Blood Flow Metab 2007;27(5):1064–1071.
32. Młodzikowska-Albrecht J, Steinborn B, Zarowski M. Cytokines, epilepsy and epileptic drugs: is there a mutual influence? Pharmacol Rep 2007;59(2):129–138.
33. Kim SS, Chang KH, Kim ST, et al. Focal lesion in the splenium of the corpus callosum in epileptic patients: antiepileptic drug toxicity? AJNR Am J Neuroradiol 1999;20(1): 125–129.
34. da Rocha AJ, Reis F, Gama HP, et al. Focal transient lesion in the splenium of the corpus callosum in three non-epileptic patients. Neuroradiology 2006;48(10):731–735.
35. Mirsattari SM, Lee DH, Jones MW, Blume WT. Transient lesion in the splenium of the corpus callosum in an epileptic patient. Neurology 2003;60(11):1838–1841.
36. Polster T, Hoppe M, Ebner A. Transient lesion in the splenium of the corpus callosum: three further cases in epileptic patients and a pathophysiological hypothesis. J Neurol Neurosurg Psychiatry 2001;70(4):459–463.
37. Anneken K, Evers S, Mohammadi S, Schwindt W, Deppe M. Transient lesion in the splenium related to antiepileptic

drug: case report and new pathophysiological insights. Seizure 2008;17(7):654–657.

38. Cohen-Gadol AA, Britton JW, Jack CR Jr, Friedman JA, Marsh WR. Transient postictal magnetic resonance imaging abnormality of the corpus callosum in a patient with epilepsy: case report and review of the literature. J Neurosurg 2002;97(3):714–717.

39. Maeda M, Shiroyama T, Tsukahara H, Shimono T, Aoki S, Takeda K. Transient splenial lesion of the corpus callosum associated with antiepileptic drugs: evaluation by diffusion-weighted MR imaging. Eur Radiol 2003;13(8):1902–1906.

40. Verrotti A, Basciani F, Trotta D, Greco R, Morgese G, Chiarelli F. Effect of anticonvulsant drugs on interleukins-1, -2 and -6 and monocyte chemoattractant protein-1. Clin Exp Med 2001;1(3):133–136.

41. Renard D, Bonafe A, Heroum C. Transient lesion in the splenium of the corpus callosum after oral corticoid therapy. Eur J Neurol 2007;14(8):e19–e20.

42. Cecil KM, Halsted MJ, Schapiro M, Dinopoulos A, Jones BV. Reversible MR imaging and MR spectroscopy abnormalities in association with metronidazole therapy. J Comput Assist Tomogr 2002;26(6):948–951.

43. Kim E, Na DG, Kim EY, Kim JH, Son KR, Chang KH. MR imaging of metronidazole-induced encephalopathy: lesion distribution and diffusion-weighted imaging findings. AJNR Am J Neuroradiol 2007;28(9):1652–1658.

44. Hunt NH, Golenser J, Chan-Ling T, et al. Immunopathogenesis of cerebral malaria. Int J Parasitol 2006;36(5): 569–582.

45. Moritani T, Ekholm S, Westesson PL, eds. Diffusion-weighted MR imaging of the brain. 2nd ed. Berlin, Germany: Springer, 2009.

46. Starkey J, Moritani T, Kirby P. MRI of CNS fungal infections: review of aspergillosis to histoplasmosis and everything in between. Clin Neuroradiol 2014;24(3):217–230.

47. Combes V, Coltel N, Faille D, Wassmer SC, Grau GE. Cerebral malaria: role of microparticles and platelets in alterations of the blood-brain barrier. Int J Parasitol 2006;36(5):541–546.

48. Milner DA Jr, Whitten RO, Kamiza S, et al. The systemic pathology of cerebral malaria in African children. Front Cell Infect Microbiol 2014;4:104. doi:10.3389/fcimb.2014.00104. Published online August 21, 2014.

49. Kobata R, Tsukahara H, Nakai A, et al. Transient MR signal changes in the splenium of the corpus callosum in rotavirus encephalopathy: value of diffusion-weighted imaging. J Comput Assist Tomogr 2002;26(5):825–828.

50. Zhang S, Feng J, Shi Y. Transient widespread cortical and splenial lesions in acute encephalitis/encephalopathy associated with primary Epstein-Barr virus infection. Int J Infect Dis 2016;42:7–10.

51. Imashuku S. Clinical features and treatment strategies of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. Crit Rev Oncol Hematol 2002;44(3):259–272.

52. Mathiesen T, Edner G, Ulfarsson E, Andersson B. Cerebrospinal fluid interleukin-1 receptor antagonist and tumor necrosis factor-α following subarachnoid hemorrhage. J Neurosurg 1997;87(2):215–220.

53. Gaetani P, Tartara F, Pignatti P, Tancioni F, Rodriguez y Baena R, De Benedetti F. Cisternal CSF levels of cytokines after subarachnoid hemorrhage. Neurol Res 1998;20(4):337–342.

54. Miller BA, Turan N, Chau M, Pradilla G. Inflammation, vasospasm, and brain injury after subarachnoid hemorrhage. Biomed Res Int 2014;(2014):384342. doi:10.1155/2014/384342. Published online July 3, 2014.

55. Butterworth RF, Giguère JF, Michaud J, Lavoie J, Layrargues GP. Ammonia: key factor in the pathogenesis of hepatic encephalopathy. Neurochem Pathol 1987;6(1-2):1–12.

56. Butterworth RF. Pathogenesis of hepatic encephalopathy and brain edema in acute liver failure. J Clin Exp Hepatol 2015;5(suppl 1): S96–S103.

57. Matsusue E, Kinoshita T, Ohama E, Ogawa T. Cerebral cortical and white matter lesions in chronic hepatic encephalopathy: MR-pathologic correlations. AJNR Am J Neuroradiol 2005;26(2):347–351.

58. Monfort P, Kosenko E, Erceg S, Canales JJ, Felipo V. Molecular mechanism of acute ammonia toxicity: role of NMDA receptors. Neurochem Int 2002;41(2-3):95–102.

59. Butterworth RF. Molecular neurobiology of acute liver failure. Semin Liver Dis 2003;23(3):251–258.

60. Jayakumar AR, Rama Rao KV, Norenberg MD. Neuroinflammation in hepatic encephalopathy: mechanistic aspects. J Clin Exp Hepatol 2015;5(suppl 1):S21–S28.

61. Rovira A, Alonso J, Córdoba J. MR imaging findings in hepatic encephalopathy. AJNR Am J Neuroradiol 2008;29(9): 1612–1621.

62. Albayram S, Ozer H, Gokdemir S, et al. Reversible reduction of apparent diffusion coefficient values in bilateral internal capsules in transient hypoglycemia-induced hemiparesis. AJNR Am J Neuroradiol 2006;27(8):1760–1762.

63. Kim JH, Choi JY, Koh SB, Lee Y. Reversible splenial abnormality in hypoglycemic encephalopathy. Neuroradiology 2007;49(3): 217–222.

64. Babanrao SA, Prahladan A, Kalidos K, Ramachandran K. Osmotic myelinolysis: does extrapontine myelinolysis precede central pontine myelinolysis? report of two cases and review of literature. Indian J Radiol Imaging 2015;25(2):177–183.

65. Takefuji S, Murase T, Sugimura Y, et al. Role of microglia in the pathogenesis of osmotic-induced demyelination. Exp Neurol 2007;204(1):88–94.

66. Hlaihel C, Gonnaud PM, Champin S, Rousset H, Tran-Minh VA, Cotton F. Diffusion-weighted magnetic resonance imaging in Marchiafava-Bignami disease: follow-up studies. Neuroradiology 2005;47(7):520–524.

67. Al Brashdi YH, Albayram MS. Reversible restricted-diffusion lesion representing transient intramyelinic cytotoxic edema in a patient with traumatic brain injury. Neuroradiol J 2015;28(4): 409–412.

68. Kim JJ, Gean AD. Imaging for the diagnosis and management of traumatic brain injury. Neurotherapeutics 2011;8(1):39–53.

69. Wong SH, Turner N, Birchall D, Walls TJ, English P, Schmid ML. Reversible abnormalities of DWI in high-altitude cerebral edema. Neurology 2004;62(2):335–336.

70. Schommer K, Bärtsch P, Knauth M, Kallenberg K. Teaching neuroimages: reversible splenial cytotoxic edema in acute mountain sickness [comment]. Neurology 2012;78(12):932.

71. Sekine T, Ikeda K, Hirayama T, Suzuki A, Iwasaki Y. Transient splenial lesion after recovery of cerebral vasoconstriction and posterior reversible encephalopathy syndrome: a case report of eclampsia. Intern Med 2012;51(11):1407–1411.

72. Gilder TR, Hawley JS, Theeler BJ. Association of reversible splenial lesion syndrome (RESLES) with anti-VGKC autoantibody syndrome: a case report. Neurol Sci 2016;37(5):817–819.

73. Ogura H, Takaoka M, Kishi M, et al. Reversible MR findings of hemolytic uremic syndrome with mild encephalopathy. AJNR Am J Neuroradiol 1998;19(6):1144–1145.

74. Takanashi J, Shirai K, Sugawara Y, Okamoto Y, Obonai T, Terada H. Kawasaki disease complicated by mild encephalopathy with a reversible splenial lesion (MERS). J Neurol Sci 2012;315 (1-2):167–169.

75. Takahashi Y, Hashimoto N, Tokoroyama H, et al. Reversible splenial lesion in postpartum cerebral angiopathy: a case report. J Neuroimaging 2014;24(3):292–294.

76. Moritani T, Capizzano A, Kirby P, Policeni B. Viral infections and white matter lesions. Radiol Clin North Am 2014;52(2): 355–382.

77. Ishikura R, Ando K, Hirota S, Okamoto N, Fatterpekar G, Sacher M. Callosal and diffuse white matter lesions with restricted water diffusion in hemophagocytic syndrome. Magn Reson Med Sci 2010;9(2):91–94.