 Imaging of the Confused Patient: Toxic Metabolic Disorders
Dara G. Jamieson, M.D. Weill Cornell Medicine, New York, NY

The patient who presents with either acute or subacute confusion, in the absence of a clearly defined speech disorder and focality on neurological examination that would indicate an underlying mass lesion, needs to be evaluated for a multitude of neurological conditions. Many of the conditions that produce the recent onset of alteration in mental status, that ranges from mild confusion to florid delirium, may be due to infectious or inflammatory conditions that warrant acute intervention such as antimicrobial drugs, steroids or plasma exchange. However, some patients with recent onset of confusion have an underlying toxic-metabolic disorders indicating a specific diagnosis with need for appropriate treatment. The clinical presentations of some patients may indicate the diagnosis (e.g. hypoglycemia, chronic alcoholism) while the imaging patterns must be recognized to make the diagnosis in other patients.

Toxic-metabolic disorders constitute a group of diseases and syndromes with diverse causes and clinical presentations. Many toxic-metabolic disorders have no specific neuroimaging correlates, either at early clinical stages or when florid symptoms develop. However, some toxic-metabolic disorders have characteristic abnormalities on neuroimaging, as certain areas of the central nervous system appear particularly vulnerable to specific toxins and metabolic perturbations. Areas of particular vulnerability in the brain include: 1) areas of high-oxygen demand (e.g. basal ganglia, cerebellum, hippocampus), 2) the cerebral white matter and 3) the mid-brain.

Brain areas of high-oxygen demand are particularly vulnerable to toxins that interfere with cellular respiratory metabolism. Preferential involvement of the basal ganglia [striatum (caudate and putamen), globus pallidus, substantia nigra, subthalamic nucleus] is found in multiple toxic encephalopathies, including poisoning with carbon monoxide, methanol, and cyanide, which impair mitochondrial cellular respiratory enzymes. The basal ganglia may be preferentially affected in patients with liver dysfunction, hypoxic-ischemic brain damage, severe glucose abnormalities and mitochondrial disorders.

Leukoencephalopathy with myelin damage may be caused by exposure to a wide variety of agents and conditions, including hypertension; CNS irradiation; therapeutic agents including cancer therapies; substance of abuse including cocaine, heroin and alcohol; and environmental toxins, such as toluene and other organic solvents. [Table 1] Cancer chemotherapeutic agents that can cause of leukoencephalopathy include methotrexate, especially with intrathecal delivery, and carmustine. Drugs implicated in acute leukoencephalopathy due to posterior reversible encephalopathy syndrome (PRES) include cyclosporine and tacrolimus.

Symmetric midbrain lesions are seen in several toxic-metabolic disorders, although other regions, such as the diencephalon and the basal ganglia may also be involved. Intoxication with ethylene glycol and methanol may affect the midbrain; and chronic alcohol abuse, as seen in Wernicke’s encephalopathy, involves areas surrounding the third ventricle and aqueduct, the mamillary bodies and the tectal plate. Metabolic disorders such as Kearns-Sayers syndrome and adult onset X-linked adrenoleukodystrophy, as well as hepatic disease, including Wilson’s disease, have distinct midbrain involvement.
Metabolic Diseases

Mitochondrial disorders are multisystem diseases involving the central nervous system, as well as multiple other organs, due to mutations in mitochondrial DNA or nuclear DNA, resulting in impairment of the function of the respiratory-chain, oxidative phosphorylation, pyruvate dehydrogenase complex or beta-oxidation. [Table 2]. The most common MRI abnormalities in mitochondrial disorders are bilateral deep gray matter lesions and focal or widespread increased white matter signal on T2-weighted imaging and FLAIR.

Leigh syndrome (LS) is a genetically heterogeneous, mitochondrial disorder that presents within the first few years of life with progressive hypotonia, failure to thrive, and loss of milestones. Eventually brain stem and basal ganglia dysfunction leads to ataxia, eye movement abnormalities, dystonia, and bulbar symptoms. Bilateral symmetric T2-hyperintensities can be seen in the basal ganglia (principally the putamen), thalamus, red nucleus, as well as cerebral white matter, brain stem and periaqueductal regions. The lesions are similar to those in Wernicke’s encephalopathy but sparing the mamillary bodies, which are characteristically involved in Wernicke’s encephalopathy. Basal ganglia abnormalities are common in some patients with Leigh syndrome (non-SURF-1 patients) but not in others. In Leigh syndrome patients with the SURF-1 gene, the brain stem, subthalamic nuclei and cerebellum are consistently involved; whereas putaminal involvement is rare. LS SURF-1 may be the only disorder with constant bilateral involvement of the subthalamic nuclei. The absence of putaminal lesions does not exclude the diagnosis of LS.

Kearns-Sayre syndrome is a phenotypically diverse mitochondrial disorder affecting muscles, the CNS and endocrine organs, with symptoms of external ophthalmoplegia, pigmental degeneration of the retina and cardiomyopathy. MRI may be normal or may show atrophy of the cerebrum and cerebellum due to spongiform degeneration. Peripheral U fibers and the globus pallidus and thalamus bilaterally are involved. Cerebellar white matter and the dorsal brainstem including the midbrain may also demonstrate symmetrical hyperintense lesions.

MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke) causes relapsing remitting “stroke-like” episodes, typically in childhood or early adulthood. Clinical presentations in MELAS include lactic acidosis, muscle weakness, deafness, seizures and dementia. Brain imaging shows multiple symmetrical or asymmetrical infarcts, acute or chronic, involving multiple vascular territories, commonly involving parieto-occipital and parieto-temporal regions. An acute, diffuse subcortical white matter signal abnormality can be seen on T2-weighted imaging and FLAIR consistent with vasogenic edema, not an acute infarct. Basal ganglial calcification and atrophy can be found in older patients. Angiography generally reveals unremarkable vessels. MRS may demonstrate elevated lactate.

Pantothenate kinase-associated neurodegeneration (PKAN), is a genetically specific type of neurodegeneration with brain iron accumulation (NBIA), a familial or sporadic disease which presents commonly in late childhood or early adolescence with progressive dementia and corticospinal signs and extrapyramidal signs. Familial NBIA is inherited recessively and has been linked to a mutation in the pantothenate kinase (PANK2) gene on band 20p13. The characteristic T2-weighted imaging finding in patients with PKAN is “the eye-of-the-tiger sign” with bilaterally symmetrical, hyperintense signal changes in the anterior medial globus pallidus, with surrounding hypointensity in the globus pallidus. This sign is not seen in patients without the PANK2 gene mutation. Pathologic changes in the central globus pallidus are due to gliosis,
demyelination, neuronal loss, and axonal swelling. Iron deposition due to loss of signal causes the surrounding hypointensity on T2-weighted imaging. While MR imaging abnormalities outside the globus pallidus are more common and more severe in mutation-negative patients, no specific MR imaging changes are found in mutation-negative patients with NBIA.

**Wilson's disease** is an autosomal recessive disorder of copper metabolism caused by a deficiency of ceruloplasmin, the serum transport protein for copper, leading to excessive copper deposition in multiple organs including the brain. The brain on MRI may appear normal or mildly atrophic, especially in asymptomatic patients. The MRI of symptomatic patients may show hyperintensities on T2-weighted sequences (isointense or hypointense on T1) in the thalami, basal ganglia, dentate nuclei, and brainstem (midbrain, pontine tegmentum). In the midbrain, the characteristic “face of the giant panda” sign on T2-weighted images is formed by hyperintense signal in the tegmentum, normal signal in the red nuclei (shifted rostrally) and in the lateral portion of the pars reticularis of the substantia nigra, with marked hypointensity of the superior colliculus.

**Metabolic Derangement**

**Posterior reversible encephalopathy syndrome (PRES)** is misnamed as it is not exclusively posterior, nor is it always reversible. In fact, untreated PRES can cause ischemic and hemorrhagic strokes and death. Well known manifestations of this protean disorder are hypertensive encephalopathy and pre-eclampsia/ eclampsia. The underlying pathology is vasogenic edema on the basis of vasoconstriction and/or cerebral hyperperfusion. The syndrome has diverse clinical & radiographic presentations, as well as multiple etiologies (e.g. hypertension, pregnancy, renal disease, malignancy, organ transplantation on immunosuppressive medications, metabolic disorders). Presenting symptoms, which generally last for days, include headache, seizures, encephalopathy, and visual symptoms. PRES on MRI shows multifocal T2-FLAIR hyperintensities (consistent with vasogenic edema). Lesions are commonly seen in parietal and occipital white matter but can involve other areas: cortex, thalamus, basal ganglia, cerebellum, brainstem and spinal cord. As characteristic of vasogenic edema, PRES is not usually not apparent on DWI sequences. DWI changes in PRES maybe related to accompanying seizures or ischemic changes, which are associated with worse prognosis as the underlying cause is not treated. Mass effect associated with vasogenic evolving to cytotoxic edema can be seen. Hemorrhage, which can be subtle or massive, may be seen on GRE sequences. Subcortical “gyral” enhancement can be seen secondary to breakdown of the blood-brain barrier. Clinical recovery occurs in most patients within days, as the underlying hypertension or metabolic abnormality is corrected. Untreated, PRES can lead to ischemic stroke, intracerebral hemorrhage, coma, and death.

**Osmotic demyelination** [central pontine myelinolysis (CPM) with extrapontine myelinolysis (EPM)] is a syndrome with a varied clinical presentation, depending on the location of involvement, due to the effect on the brain of changes in extracellular fluid osmolality. Osmotic demyelination can be associated with electrolyte shifts, including both hyponatremia and hypernatremia, either rapid, slow or no correction, and can be seen in the setting of severe hyperglycemia. The clinical picture of osmotic demyelination syndrome ranges from mild spasticity to coma, depending on the extent and location of the
demyelinating lesions. The pons is generally, but not exclusively affected, possibly related to the susceptibility of tightly packed pontine fiber tracts to fluid shifts. Characteristically focal T2 prolongation signal abnormality involving the central pons is seen without associated enhancement or mass effect. However, demyelination is not restricted to the pons and may affect the cerebral and spinal white matter, as reflected in shift in nomenclature from central pontine myelinolysis to pontine and extrapontine myelinolysis to the present, non-localizing term “osmotic demyelination.” Pathologically, there is loss of the myelin sheath with relative sparing of axons and neurons in sharply demarcated, non-inflammatory lesions. The white matter lesions may persist years after exposure, despite clinical recovery. Chronically, a hypodensity on CT scan and an abnormal high signal on FLAIR can be seen in the central pons, without mass effect or enhancement, representing gliosis from a previous episode of osmotic demyelination.

**Hepatic encephalopathy** can occur in the setting of acute fulminant hepatic failure, such as with acetaminophen overdose, or as a more chronic process in patients with hepatocellular dysfunction (portal-systemic shunting). Acute hepatic encephalopathy can be rapidly fatal, whereas chronic liver disease is usually a more indolent process causing neuropsychiatric symptoms. Diffuse cerebral edema can be a subtle finding on CT or MRI, even in the early stages of clinical manifestations of encephalopathy. Bilateral, symmetrical T1 signal hyperintensity in the substantia nigra, red nucleus, and tectum, with similar changes in the basal ganglia, subthalamic nucleus, and adenohypophysis, are due to increased brain tissue concentration of manganese. Diffuse cortical edema and hyperintensity on T2-weighted images, with sparing of the perirondal and occipital regions are seen with florid hepatic encephalopathy. With survival the MRI hyperintensities may resolve with residual diffuse atrophy. The increased intracellular osmolality caused by hyperammonemia results in a reduction of choline and myoinositol peaks, and a rise in the glutamine and glutamate peaks, on MR spectroscopy.

**Hypoglycemic encephalopathy** producing MRI lesions may be seen in diabetics who overdose on oral hypoglycemic agents or insulin or in nondiabetic patients with an undiagnosed insulinoma of the pancreas, with the extent of brain damage depending on the severity and duration of hypoglycemia. With severe hypoglycemia bilateral T2 hyperintensities are seen in the temporal, occipital, and insular cortex, the hippocampi, and the basal ganglia. In some cases of milder, reversible hypoglycemia, transient, isolated white matter abnormalities involving the splenium of the corpus callosum, internal capsules, and corona radiata are seen on T2-weighted images. Lesions may show restricted diffusion. The brainstem, cerebellum and thalamis are characteristically spared.

**Hypoxic-ischemic encephalopathy (HIE)** usually results from a precipitous drop in cerebral perfusion in the setting of severe hypotension or cardiac arrest and subsequent resuscitation. Severe sustained hypoglycemia, prolonged seizure activity, profound carbon monoxide poisoning, or severe hypoxemia due to pulmonary disease such as massive pulmonary embolism can mimic hypoxic–ischemic brain injury. The brain has high demand for energy supply (with only 2% of the body mass the brain requires 15% of the body’s energy supply), but has very few energy reserves of its own. The mechanism of cell damage due to energy depletion in brain cells (especially neurons) consists of early Na⁺/K⁺ pump failure. Subsequently the release of neurotoxic glutamate results in osmotic intracellular edema, then Ca²⁺ influx into the damaged cells and release of free radicals, with eventual cell death by either necrosis or apoptosis.
Different cells types exhibit differential vulnerability to hypoxic-ischemic damage based on their metabolic demands and their ability to survive in the absence of an adequate energy supply. Among primary brain cells, neurons are the most susceptible, followed by oligodendrocytes, then astrocytes. Specific subsets of neurons are also selectively vulnerable, leading to characteristic imaging patterns with hypoxic-ischemic encephalopathy. The most vulnerable neurons are the pyramidal cells of the CA1 region of the hippocampus, the pyramidal neurons of the neocortex (layers 3, 5, 6), the Purkinje cells of the cerebellum, and striatal neurons. The pathologic manifestations of HIE depend on the severity and duration of the insult, as well as individual vulnerability and pre-morbid conditions. Initially there are changes in the color and morphology of the nuclei and cytoplasm of neurons (red cytoplasm and pyknotic shrunken nuclei). With more severe and sustained cerebral hypoperfusion, dropout of neurons, gliosis and a selective laminar necrosis of the cortical layers, hippocampal atrophy and sclerosis are seen. In HIE there is preferential involvement of border zone or watershed areas at the junction between two main arterial territories (anterior-middle cerebral artery distribution, or middle-posterior cerebral artery distributions). In these areas of anatomical vulnerability there is an absence of anastomotic circulation between the different territories leading to more severe damage in areas that serve as terminal areas between two circulations and the susceptibility to drop in arterial pressure in the circulation. Borderzone or end-vessel cerebral infarctions can occur in patients who survived cardiac arrest or severe hypotension. Another pathologic product of HIE is the mislabeled “respirator brain” (correctly called “non-perfused” brain) which usually occurs in brains that are subjected to increased intracranial pressure of any cause. Once arterial circulation stops, brain death occurs and the non-perfused brain is found to be severely macerated on pathological examination.

Brain imaging in HIE, which can be entirely normal or show characteristic anatomic patterns, depending on the severity of the hypoxic-ischemic injury and the timing of imaging, can be used to prognosticate. An MRI will be much more sensitive in detecting subtle cellular injury, although the logistics of obtaining an MRI on a hemodynamically unstable, intubated patient limit its usefulness in prognostication. A patient with a clinically poor prognosis can have an unremarkable MRI scan, but the presence of a marked abnormality on MRI bodes ill for functional recovery. In the initial days after hypoxic-ischemic brain injury, ischemia and cytotoxic edema may be seen on brain imaging. The CT scan of the head may show diffuse swelling with effacement of the basal cisterns, ventricles and sulci, decreased grey–white matter cortical distinction, and hypodensity of the cortical grey matter and basal ganglia. Hypodensity of the white matter may be seen due to distension of the deep medullary veins and consequent obstruction of the venous drainage. Focal areas of infarction may develop in the basal ganglia, cortical boundary zone territories or territories of distal perfusion such as the bilateral calcarine corticies. On MRI of patients with poor prognosis, DWI and FLAIR images may initially show widespread hyperintensity consistent with ischemia in subcortical grey matter structures, as well as in the cortex and subcortical white matter, cerebellum and hippocampus. In the subacute phase, as the cerebral edema resolves, the DWI hyperintensity may persist or pseudo-normalize. Extensive abnormalities may be seen on T2-weighted and FLAIR images in both gray and white matter. Infarcts may be noted in areas of vulnerability due to
anatomy (border-zone or distal territories) or increased metabolic demands (basal ganglia, cerebellum, hippocampus). Diffuse atrophy and cortical laminar necrosis may be seen if the patient survives, generally in a neurologically devastated state.

Vitamin Deficiencies

**Vitamin B12 deficiency** (“pernicious anemia”) presents with peripheral neuropathy, optic neuropathy, and encephalopathy. Macrocytic anemia is not always present and symptoms may be precipitated by nitrous oxide exposure. T2 and FLAIR hyperintense lesions are seen preferentially along the thoracic cord or diffusely, with characteristic involvement of the pyramidal tracks and posterior columns (subacute combined degeneration). Patients with chronic myelopathy may have spinal cord atrophy. T2 and FLAIR hyperintensities can be seen in the cerebral white matter and around the fourth ventricle.

**Vitamin E deficiency** can occur with intestinal malabsorption syndromes and abetalipoproteinemia (Bassen-Kornzweig syndrome). The loss of the anti-oxidant action of alpha tocopherol, the active form of vitamin, can result in loss of dorsal ganglionic neurons with degeneration of their peripheral and central axons (causing a sensory peripheral neuropathy and ataxia respectively). MRI of the spine can show high-signal lesions on T2-weighted images in the posterior columns, correlating well with the clinical presentation.

**Wernicke’s encephalopathy** is an acute neurological disease resulting from thiamine (vitamin B1) deficiency seen in patients with multiple causes of nutritional depletion, including in chronic alcoholics and in patients who have undergone gastric bypass procedures without thiamine repletion. The MRI changes may result from defective blood-brain barrier in periventricular regions that have a high rate of thiamine related glucose and oxidative metabolism. The clinical manifestations include oculomotor abnormalities (i.e. oculoparesis, nystagmus), gait ataxia, and encephalopathy, and are treated with high-dose parenteral thiamine. The MRI in patients with Wernicke’s syndrome may be normal or may show symmetrical T2-hyperintense in thalamic areas surrounding the 3rd ventricle and aqueduct, in the mamillary bodies, and in tectal plate. Enhancement of the mamillary bodies may be seen on T1-weighted sequences and is highly specific, but not sensitive, for acute Wernicke’s encephalopathy. The periventricular hyperintense areas in the diencephalon, the medial thalamic nuclei and the periaqueductal gray are correlated with spongy disintegration on pathological examination.

Toxicities of substances of abuse

**Chronic alcohol abuse** is associated with multiple syndromes with neuroimaging correlates. As compared to non-alcoholics, persons with chronic alcoholism have a disproportionate decrease in cerebral (especially frontally) and cerebellar white matter on MRI and CT imaging, and an increased number of white matter hyperintense lesions on MRI.

**Alcoholic cerebellar degeneration** produces relatively selective lower-extremity ataxia in individuals with chronic alcohol abuse. The toxic effects of chronic alcohol use, in combination with vitamin B1 deficiency due nutritional deficits and inhibited thiamine absorption from small intestine, cause degeneration of the anterior superior vermis and adjacent hemispheres, the parts of the cerebellum that mainly receive spinal
Imaging of the Confused Patient: Toxic-Metabolic Disorders

CT and MRI studies in chronic alcoholism can show atrophy of the cerebellar vermis; although, alcoholics may have imaging evidence of cerebellar atrophy without clinically evident gait ataxia.

Marchiafava-Bignami syndrome is associated with severe chronic alcoholism and malnourishment. Dementia, dysarthria and a spastic gait disorder may be seen in combination with Wernicke’s encephalopathy. Characteristic T1 hypointense and T2 hyperintense lesions are found in the corpus callosum, centrum semiovale, and periventricular white matter. The white matter atrophy, which often includes the corpus callosum, may be partially reversible.

Illicit drug exposure may produce characteristic neuroimages; although determination of the specific neurotoxic agent may be problematic. Patients who present with suspected ingestion of one or more illicit drugs may also have chronic or acute exposure to other neurotoxic agents, including alcohol, that hamper the association between a specific agent and a particular clinical and neuroimaging characteristic. An accurate evaluation of polysubstance abuse may not be reflected in toxicology screening, which may be performed late after exposure or be insensitive to the involved agent(s). Some illicit drugs have delayed toxic manifestations, with clinical and imaging presentations occurring distant from the acute or chronic exposure. While acute diffuse white matter changes (leukoencephalopathy) are seen in patients who present with suspected drug abuse, the exact cause of the MRI finding may be difficult to determine.

Cocaine can cause vasospasm and vasculopathy leading to ischemic and hemorrhagic infarction. Lesions with increased signal intensity on T2-weighted images are reported in the globus pallidi, the hippocampi, splenium, and cerebral white matter, with affected regions often showing restricted diffusion, consistent with ischemia from cocaine-induced vasculopathy, with ingestion remote from the time of presentation. The globus pallidus is most vulnerable to the vasculotoxic effects of cocaine. Cocaine can also produce a toxic leukoencephalopathy from direct toxic effects after IV or inhalational use, or when combined with other prescription and/or recreational drugs. The effects of cocaine can be remote due to arterial changes (i.e. vasculopathy) or direct with rhomboencephalitis due to cocaine-induced bony erosion of the skull base.

Amphetamine derivates, such as 3,4-methylenedioxymetamphetamine (MDMA or ecstasy) or methamphetamine, that are abused as psychostimulants do not have specific neuroimaging correlates. Polysubstance abuse by amphetamine users may complicate efforts to isolate neuroimaging characteristics of individual abused substances. However, the recreational use of amphetamines has been associated with gray matter atrophy and an increased number and size of white matter lesions seen on T2-weighted imaging on MRI.

Heroin neurotoxicity has multiple manifestations depending on the method of ingestion. Intravenously heroin can result in cerebral infarcts in distal arterial territories, with or without associated valvular heart disease. A spongiform leukoencephalopathy can develop after repeated inhalation of heroin vapors (“chasing the dragon”), although the clinical syndrome and the MRI changes can be seen after a heroin single exposure. The exact heroin-related toxin responsible for the dose-response relationship between the level of exposure and the severity of the neurological impairment with characteristic neuroimaging correlates is unknown. Neurological symptoms of cerebellar ataxia, altered mental status and psychiatric disorders progress may occur acutely or subacutely. Symmetrically hyperintense areas within parieto-occipital subcortical and cerebellar white matter, the cerebellar peduncles, the splenium
of the corpus callosum, and the posterior limb of the internal capsules are seen on T2-weighted and FLAIR images. The anterior limb of the internal capsules are generally spared. There is often selective, symmetric involvement of the corticospinal tract, the medial lemniscus, and the tractus solitaries. The white matter changes may resolve with residual atrophy in patients with clinical improvement with recovery after the ingestion. MR spectroscopy in patients with leukoencephalopathy from inhalational heroin ingestion can show increased lactic acid and myo-inositol, decreased N-acetyl aspartate and creatine, normal to slightly decreased choline, and normal lipid peak. Neuropathologically, spongiform degeneration of the white matter is associated with multivacuolar degeneration of the oligodendrocytes.

**Methadone** toxicity has been reported cause an acute leukoencephalopathy, presenting as symmetric and confluent high-signal-intensity changes in the cerebral white matter on T2-weighted and FLAIR images with, with sparing of the subcortical U-fibers. Brainstem and cerebellar changes seen with acute leukoencephalopathy with inhalational heroin, may not be seen with methadone toxicity. A decrease of the N-acetyl aspartate peak with a relative increase of the choline peak, similar to findings reported in inhaled heroin neurotoxicity, can be found on MR spectroscopy.

**Toluene** is a highly lipophilic organic solvent, found in paints, glues, inks and paint thinner, with exposure with intoxication occurring occupationally or recreationally to produce chronic or acute intoxication. Toluene can be inhaled for a sensation of euphoria ("glue sniffing"). Toluene toxicity can produce dementia, progressive cerebellar dysfunction, visual loss due to optic atrophy, pyramidal tract signs, and cranial nerve abnormalities. Chronic toluene abuse is characterized by gray matter hypointensity on T2-weighted imaging, involving the cerebral cortex, deep central nuclei, brainstem and cerebellum, likely related to iron deposition. The MRI shows multifocal white matter T2 hyperintensities in the periventricular and subcortical white matter and in the upper cervical cord. MR spectroscopy may show decreased N-acetyl aspartate and increased myo-inositol in the cerebellar white matter and centrum semiovale. Atrophy on MRI can be seen diffusely as well as in the corpus callosum and cerebellum, after recovery from the period of exposure.

**Environmental Toxin Exposure**

**Carbon monoxide** (CO) competitively binds to hemoglobin (carboxyhemoglobin) causing hypoxemia with reduced the oxygen-carrying capacity of the blood and decreased release of oxygen to tissue. CO also has direct mitochondrial toxicity, inhibiting electron transport through its effect on mitochondrial cytochrome oxidase. CO intoxication can produce a distinct radiological picture with the appearance of signs and symptoms occurring days after the acute exposure. Acute imaging with CT or MRI may be unremarkable prior to development of persistent focal lesions and/or generalized atrophy. Hypodensities in the putamen, frontal lobes and the centrum semiovale may be seen with early CT scanning, which may dissipate or persist. T2 hyperintensity in the basal ganglia is typical in acute poisoning, often with restricted diffusion on diffusion-weighted images. The cerebral white matter or the corpus callosum may be involved with increased signal on DWI. Several weeks after the exposure CT with contrast may show enhancing lesions within the putamen, globus pallidus, and dentate nucleus bilaterally. Delayed leukoencephalopathy and globus pallidus lesions can be seen on MRI many weeks to
months after the acute exposure, coincident with gradual delayed cognitive decline. Bilateral, symmetric necrosis of the globus pallidus is the most common brain injury persistent after carbon monoxide poisoning. These lesions appear hypointense on T1-weighted and hyperintense on T2-weighted images and may be present years after survival. The caudate, putamen, thalamus, hypothalamus, temporal lobe, cerebellum and cerebral white matter may be involved.

**Cyanide** poisoning can occur by inhalation, ingestion, or absorption through the skin. Chronic intoxication occurs with occupational exposure; but, acute intoxication is generally due to intentional ingestion. Nausea, headache and dizziness, with ataxia and optic neuropathies, can occur with low-level toxicity; but, higher exposures produce metabolic acidosis, hyperventilation, loss of consciousness, cardio-respiratory arrest, coma and death. Cyanide blocks the trivalent iron in the cellular respiration enzymes so that the oxygen released by oxyhemoglobin cleavage can no longer be bound. Because the cyanide ion blocks oxidative respiration causing tissue hypoxia, areas of the brain with a high oxygen requirement, such as the basal ganglia, are particularly vulnerable, and show imaging abnormalities. On T1-weighted sequences on MRI, multiple hypointense areas are seen within the globus pallidus and posterior putamen. Hemorrhagic necrosis in the basal ganglia, similar to that seen in methanol intoxication, can be seen. Because of their high degree of oxygen dependency, the cerebellum and sensorimotor cortex can also be affected. Despite its high oxygen requirement, the hippocampus is generally spared in cyanide toxicity. Acute cyanide intoxication typically causes a rapidly evolving brain edema, followed by long-term atrophy, if the exposure was survivable. Delayed development of basal ganglia lesions may correlate with a Parkinsonian syndrome, as well as memory impairment, in survivors of acute cyanide toxicity.

**Methanol** ingestion can be fatal due to its CNS depressant properties and its metabolism to formate via by alcohol dehydrogenase in the liver. Formate is toxic because it inhibits mitochondrial cytochrome c oxidase, causing cellular hypoxia. Metabolic acidosis and blindness due to optic neuropathy are characteristic of methanol ingestion. Bilateral hemorrhagic necrosis of the putamen is the most characteristic finding with survival after accidental or intentional methanol ingestion. Increased T2-weighted signal intensity in the putamen, with variable T1-weighted signal (dependent on the presence and stage of hemorrhage) and enhancement are seen. Putaminal hemorrhage indicates a poor prognosis, with evolution to cystic necrosis in survivors. Other areas of involvement include the basal ganglia, subcortical white matter, brainstem tegmentum, and the cerebellum.

**Ethylene glycol** is usually ingested intentionally as a suicide attempt. The typical MR features of ethylene glycol toxicity include symmetrical hyperintense lesions on T2-weighted images of the basal ganglia, thalamus, amygdala, hippocampus, and frontal white matter. Involvement of the white matter tracts with restricted diffusion may also be present. The typical MR features of ethylene glycol toxicity are symmetrical hyperintense lesions on T2-weighted images of the basal ganglia, thalamus, amygdala, hippocampus, and frontal white matter.

**Medication or Treatment Toxicity**

**Valproic acid (VPA)** toxicity causes progressively altered mental status with evolution from encephalopathy to coma due to drug overdose or VPA-related hyperammonemic encephalopathy, which may
occur on therapeutic doses. VPA toxicity may be due to inhibition of the urea cycle within the liver and/or stimulation of glutaminase within the renal cortex, resulting in increased glutamine uptake and ammonia release. VPA overdose has been associated with bilaterally increased T2 signal within the globus pallidus, as well as in cerebellar white matter and frontal/temporal/insular cortex. Diffuse hyperintensity on T2-weighted and FLAIR images in the white matter, cortex, and pons, as well as unilateral lesions in the putamen and caudate nucleus, have been reported. Both cytotoxic (evident on DWI) and vasogenic (evident on FLAIR) edema may be found with VPA toxicity. MR imaging abnormalities associated with hepatic encephalopathy, including bilateral high signal intensities in the globus pallidi on T1-weighted images due to increased tissue manganese, may be seen with VPA toxicity. MR spectroscopy may show decreased myoinositol and choline, and increased glutamine consistent with VPA toxicity.

Metronidazole in high doses can produce weakness and altered mental status. Characteristic bilateral, symmetric involvement of the dentate nuclei causes cerebellar symptoms of dysarthria and gait ataxia. The tectum, red nucleus, periaqueductal gray matter, and dorsal pons are involved, with less common involvement of the dorsal medulla and the corpus callosum. Hyperintensities on T2-weighted images do not enhance on T1-weighted imaging and may reverse after discontinuation of metronidazole.

Lithium is used to treat bipolar disorder, and less commonly, headache disorders such as hypnic and cluster headaches. The most common symptom of lithium toxicity is a rapid postural, sustention and action tremor. Neuromuscular effects of increased lithium levels include proximal muscle weakness, rhabdomyolysis, a myasthenia gravis-like illness, and an axonal neuropathy. Lithium has a narrow therapeutic range, necessitating close monitoring of serum lithium concentrations, especially in the setting of diuretic use, nausea and vomiting, and surgery. The signs and symptoms of lithium toxicity can develop insidiously until mild confusion progresses to the development of florid signs of encephalopathy. Lithium associated encephalopathy is characterized by altered mental status, dysarthria, ataxia, and nystagmus. The Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT) includes neurologic symptoms induced by lithium toxicity that persist after the discontinuations of the drug. While fever and acutely elevated lithium levels are often seen in SILENT, this syndrome may develop even with therapeutic lithium levels. Cerebellar symptoms are most frequently reported with SILENT but extrapyramidal, cognitive, and brainstem dysfunction have also been reported. Persistent neurologic deficits often become apparent after the improvement in alteration of consciousness or encephalopathy. Some of neurological deficits may eventually spontaneously recover, but generally the neurological sequelae of SILENT persist. Neuroimaging of patients with cerebellar symptoms of SILENT may show cerebellar atrophy, not necessarily correlating with the severity of cerebellar symptoms. The pathophysiological processes causing the cerebellar manifestation of SILENT are unclear; but, the cerebellar dysfunction may be related to delayed gene expression resulting in Purkinje cell drop-out and cerebellar demyelination, triggered by exposure to lithium, with symptoms often becoming evident after recovery from acute intoxication.

Cyclosporine toxicity in solid organ transplant patients may present with headache, altered mental status, visual disturbance, and seizures. Areas of hyperintensity on T2-weighted and FLAIR images are seen in the subcortical white matter of the posterior temporal, parietal, and occipital lobes, with occasional involvement
of the frontal lobes. The lesions characteristically show vasogenic edema characteristic of PRES, which is also seen with tacrolimus toxicity.

**Cranial irradiation** can produce a leukoencephalopathy which is most common in long-term survivors who underwent whole brain radiation. Irradiation can produce an acute reaction involving patchy, reversible edema of the white matter; a delayed reaction with widespread edema and demyelination; and a severe delayed reaction involving the loss of myelin and axons as a result of vascular necrosis and thrombosis. Stroke-like migraine attacks after radiation therapy (SMART) occurs as a delayed consequence of cerebral irradiation. Patients with SMART have prolonged, reversible neurological signs and symptoms including confusion, visual changes, hemi motor and sensory deficits, aphasia, seizures, and headaches. Transient, diffuse, unilateral cortical enhancement of cerebral gyri in the area of irradiation is seen on MRI.

Table 1  **Toxic Leukoencephalopathies** (adapted from Filley & Kleinschmidt-DeMaster)

**Antineoplastic agents**
- methotrexate, carmustine, cisplatin, cytarabine (Ara-C), fluorouracil, levamisole, fludarabine, thiopeta, interleukin-2, interferon alpha

**Cranial irradiation**

**Immunosuppressive agents**
- cyclosporine, tacrolimus

**Antimicrobial agents**
- amphotericin B, hexachlorophene

**Drugs of abuse**
- toluene, ethanol, cocaine, 3,4-methylenedioxymethamphetamine, intravenous heroin, inhaled heroin / “chasing the dragon,” pyrolysate, psilocybin, methadone

**Environmental toxins**
- carbon monoxide, arsenic, carbon tetrachloride

Table 1  **Mitochondrial disorders** (incomplete list)

- MELAS (mitochondrial encephalomyelopathy, lactic acidosis, stroke-like episodes)
- MERRF (myoclonus, epilepsy, ragged red fibers)
- Leigh (subacute necrotizing encephalomyelopathy)
- Kearns-Sayre syndrome
- Leber hereditary optic neuropathy
- Menkes kinky hair (trichopoliodystrophy)
- Progressive external ophthalmoplegia
- Alper’s disease (progressive infantile poliodystrophy)
- Pantothenate kinase-associated neurodegeneration
- Neuropathy, ataxia, and retinitis pigmentosa (NARP)

**References**

Niethammer & Ford. Permanent lithium-Induced cerebellar toxicity: three cases and review of literature. Movement Disorders 2007; 22; 570-573.
Sutter and Kaplan What to see when you are looking at confusion: a review of the neuroimaging of acute encephalopathy. J Neurol Neurosurg Psychiatry 2015;86:446–459.