Toxic and Metabolic Diseases

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15.1 Toxic Disease

15.1.1 Chemotherapy-Induced Leukoencephalopathy

Intrathecal or intravenous methotrexate, with or without radiation therapy, can cause diffuse white matter changes [1]. There are two types of methotrexate-related leukoencephalopathy: (1) disseminated necrotizing leukoencephalopathy (DNL) and (2) mild leukoencephalopathy [2]. DNL indicates a rapidly deteriorating clinical course, with irreversible extensive white matter damage. Mild leukoencephalopathy is usually transient. MR imaging findings are different in these two types. In DNL, MR imaging shows multifocal T2 and FLAIR hyperintensities in the white matter with small irregular low-signal foci and contrast enhancement. DW imaging shows slightly increased ADC in the center of the lesion and increased ADC in the perilesional vasogenic edema [3] (Fig. 15.1). In mild leukoencephalopathy MR imaging shows diffuse T2 hyperintensity in the white matter. DW imaging shows the diffuse white matter as hyperintense with decreased apparent diffusion coefficient (ADC), even before conventional MR imaging can detect the lesions (Fig. 15.2). Pathologically the white matter lesion represents intramyelinic edema.

High-dose chemotherapy including carmustine (BCNU), cyclophosphamide, cisplatin, 5-fluorouracil (5-FU), and carmofur (a derivative of 5-FU) can also cause diffuse white matter disease. The lesions are hyperintense on T2-weighted images as well as on DW images, and ADC is decreased [4–6] (Fig. 15.3). Chemotherapeutic agents such as 5-FU and carmofur can have direct toxic effects on myelin, which causes intramyelinic edema [7]. Chemotherapy-associated leukoencephalopathy can be fatal and early diagnosis and discontinuation of the offending drug is therefore necessary. Leukoencephalopathy was found in 30% of long-term ALL survivors treated with methotrexate and persisted in 80% [8]. Furthermore, mean diffusivity in the genu of the corpus callosum, corona radiata, and the superior fronto-occipital fasciculi was associated with global neurocognitive impairment [8, 9].

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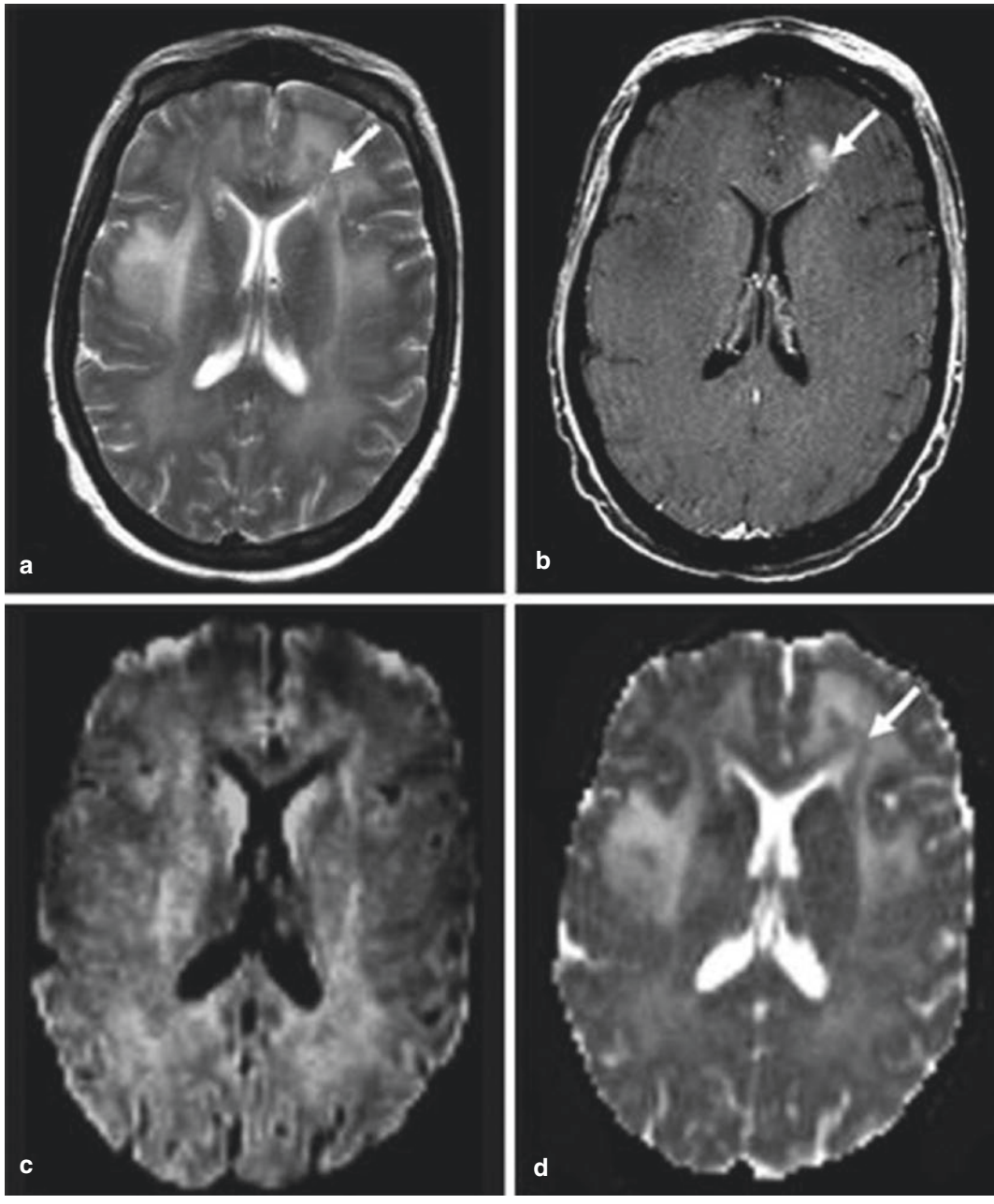


Fig. 15.1 Disseminated necrotizing leukoencephalopathy in a 43-year-old woman with leptomeningeal metastasis from breast carcinoma treated with methotrexate and radiation. (**a**) T2-weighted image shows multifocal hyperintensities in the deep white matter with small irregular low-signal foci in the left frontal area (*arrow*). (**b**) Postcontrast T1-weighted image reveals enhancement in the foci (*arrow*) in the left frontal white matter consistent with necrosis. (**c**, **d**) DWI image shows mild hyperintensity in the white matter lesions associated with diffuse increased ADC and mild increased ADCs in the left frontal foci, consistent with diffuse vasogenic edema and necrotic foci (*arrow*). (Courtesy of Policeni B, MD, University of Iowa Hospitals and Clinics, USA)

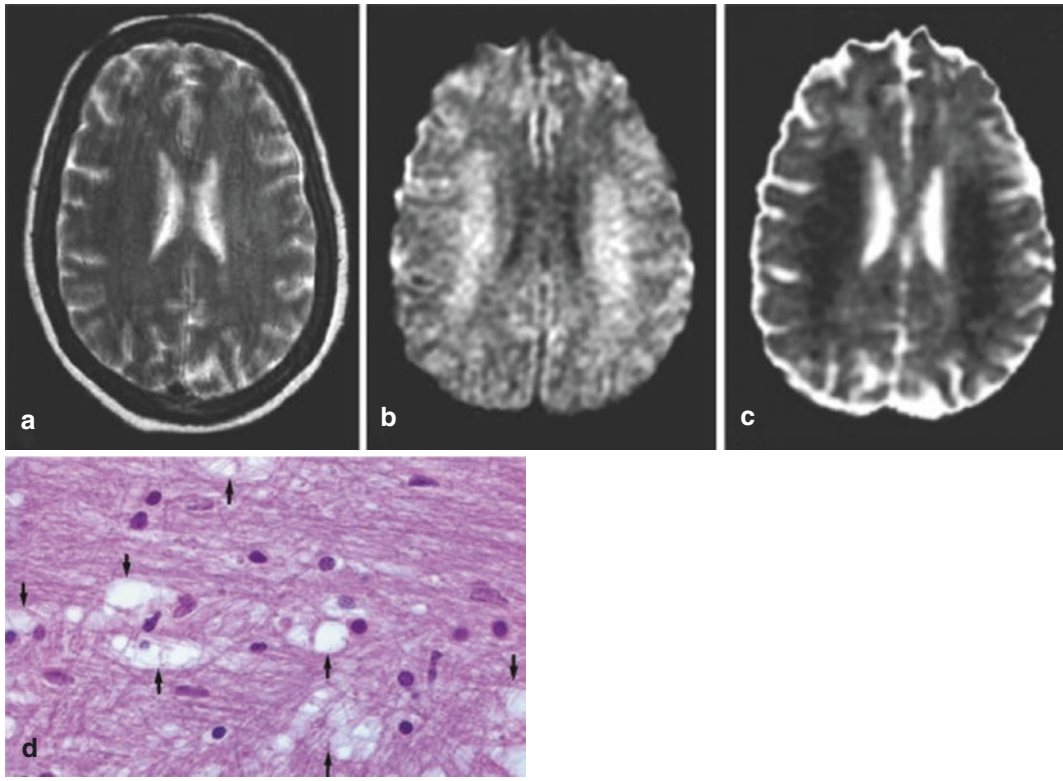


Fig. 15.2 Methotrexate leukoencephalopathy (high dose) in a 50-year-old woman. (**a**) T2-weighted image does not demonstrate an appreciable abnormality in the white matter. (**b**) DWI image shows symmetric hyperintensity in the bilateral corona radiata extending into the central semiovale. (**c**) ADC map shows white matter lesions as decreased ADC, which represents intramyelinic edema. (**d**) Pathology shows spongiform change representing intramyelinic edema (*arrows*) diffusely in white matter. Astrocytes are relatively spared (hematoxylin–eosin stain, original magnification ×200)

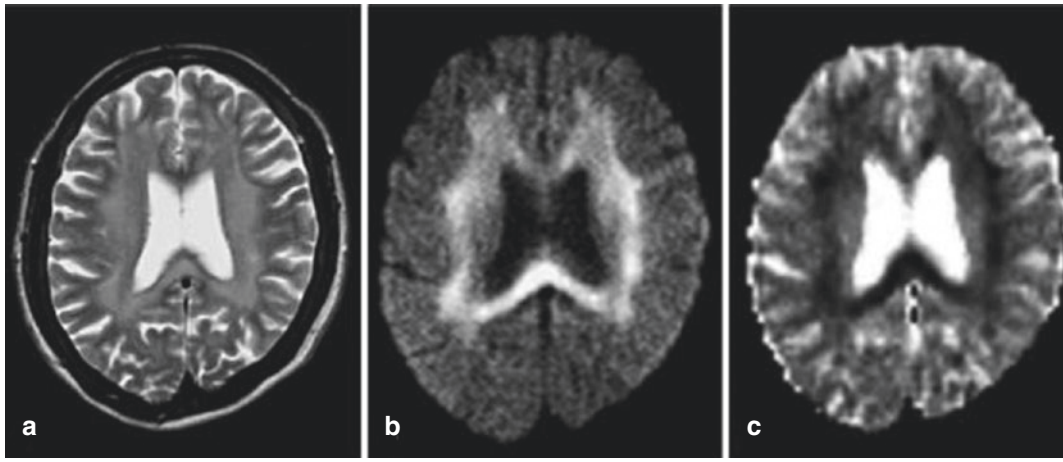


Fig. 15.3 Carmofur leukoencephalopathy in a 58-year-old woman. (**a**) T2-weighted image shows symmetric hyperintensity in the periventricular white matter including the corpus callosum. (**b**, **c**) DW image shows these lesions as hyperintense with decreased ADC, presumably related to intramyelinic edema

15.1.2 Carbon Monoxide Intoxication

The affinity of hemoglobin for carbon monoxide (CO) is approximately 250 times that of oxygen. The carboxyhemoglobin reduces the oxygen-carrying capacity of blood, causing tissue hypoxia. CO also inhibits the mitochondrial electron transport enzyme system and activates polymorphonuclear leukocytes, which causes brain lipid peroxydation and myelin breakdown. The globus pallidus is the most common site of involvement. The putamen, caudate nucleus, thalamus, hippocampus, and substantia nigra are also occasionally involved [10]. The globus pallidus and the pars reticulata of the substantia nigra contain the highest iron concentration in the brain. CO directly binds heme-iron in these areas, which is the cause of the histotoxicity and selective vulnerability of the pallidoreticularis [11]. DW imaging shows hyperintensity with decreased ADC in these lesions in the acute phase (Fig. 15.4). Cerebral white matter involvement is common and usually presents as delayed anoxic encephalopathy. It is usually seen in the late subacute phase after recovery from the acute stage of CO poisoning (with a lucid interval of usually 2–3 weeks). DW imaging shows diffuse hyperintensity with decreased ADC in the periventricular white matter and centrum semiovale [12, 13].

15.1.3 Cocaine, Phencyclidine Hydrochloride, Amphetamines, and Related Catecholaminergics

Cocaine, phencyclidine hydrochloride, amphetamines, and related catecholaminergics can cause hemorrhage or infarction due to vasculitis, vasculopathy, or acute hypertensive effects [1]. DW imaging can be useful for the detection of these lesions (see also Chap. 11).

15.1.4 Opiods (Morphine, Methadone, Oxycodone, Heroin)

Opioid overdose has been reported as a cause of delayed hypoxic leukoencephalopathy, cerebellar white matter edema (particularly with heroin and methadone) [14, 15] and symmetric pallidal and hippocampal-restricted DWI [14, 16–21]. Narcotic-induced leukoencephalopathy is not only secondary to hypoxia but to direct toxicity to the myelin-rich white matter by lipophilic drugs [22]. This toxic leukoencephalopathy may be reversible [23]. The inhalation of black-market heroin vapors (pyrolysate), practice known as "chasing the dragon," as well as intravenous consumption of heroin can lead to toxic leukoencephalopathy [24]. The leukoencephalopathy is pathologically characterized by spongiform degeneration of the white matter as a result of fluid accumulation within the myelin sheaths (intramyelinic edema). Electron microscopy shows vacuoles between the myelin lamellae by splitting of the intraperiod lines [25]. On brain MRI, it displays symmetric white matter T2 hyperintensities in the cerebrum, cerebellum, and brainstem [26] with facilitated diffusion [27] also involving the cerebral peduncles, corticospinal tracts, lemniscus medialis, and solitary tracts [28–30]. The accumulation of restricted fluid between the layers of myelin lamellae may cause hyperintensity on DW imaging with decreased ADC [31] (Figs. 15.5 and 15.6). Because the myelin itself and the blood–brain barrier are intact in cases of less severe heroin-induced leukoencephalopathy, the changes in the DW signal may be reversible on follow-up MR imaging [21].

15.1.5 Metronidazole Induced Encephalopathy

Metronidazole is an antimicrobial agent used in the treatment of protozoal and anaerobic bacterial infections and is often used in hepatic encephalopathy. Metronidazole toxicity can cause both peripheral neuropathy and central nervous system dysfunction with ataxic gait, dysarthria, seizures, and encephalopathy, which may result from both short-term and chronic use of this drug and is collectively referred to as "metronidazole induced encephalopathy." Neuroimaging is essential for the diagnosis of this uncommon entity. Typical anatomical sites of involvement include the cerebellum, midbrain, brainstem, and corpus callosum. Symmetric T2 hyperintensity of the dentate nuclei is the most suggestive feature (Fig. 15.7) [32, 33]. Diffusion restriction at the abovementioned sites has been mentioned, but ADC values

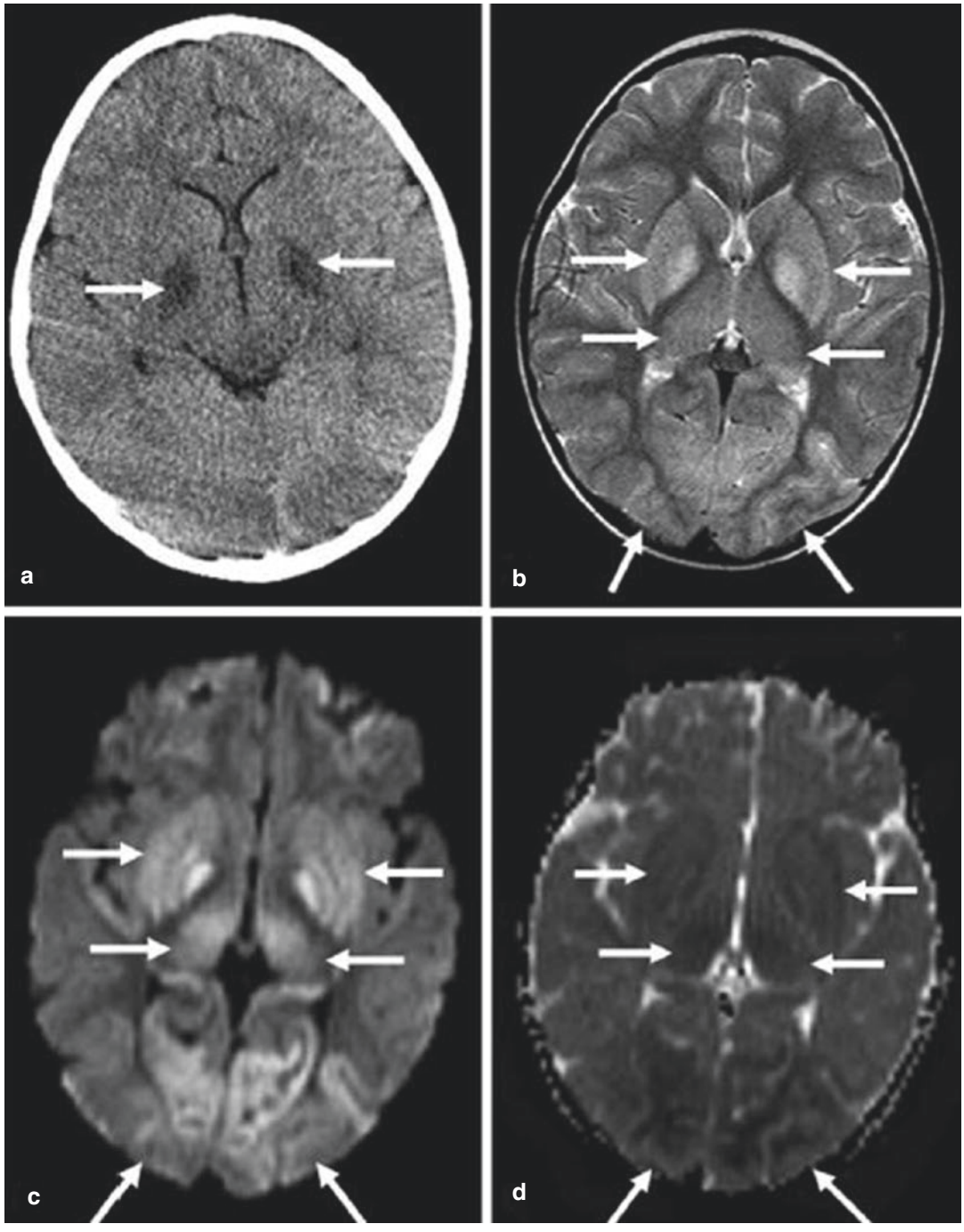


Fig. 15.4 Carbon monoxide poisoning in a 4-year-old boy. (**a**) CT shows symmetric low-density areas in the globi pallidi. (**b**) T2-weighted imaging shows symmetric extensive hyperintense lesions in the basal ganglia, thalami, hippocampi, and posterior cerebral cortices. (**c**, **d**) DW image shows these areas as hyperintense with decreased ADC

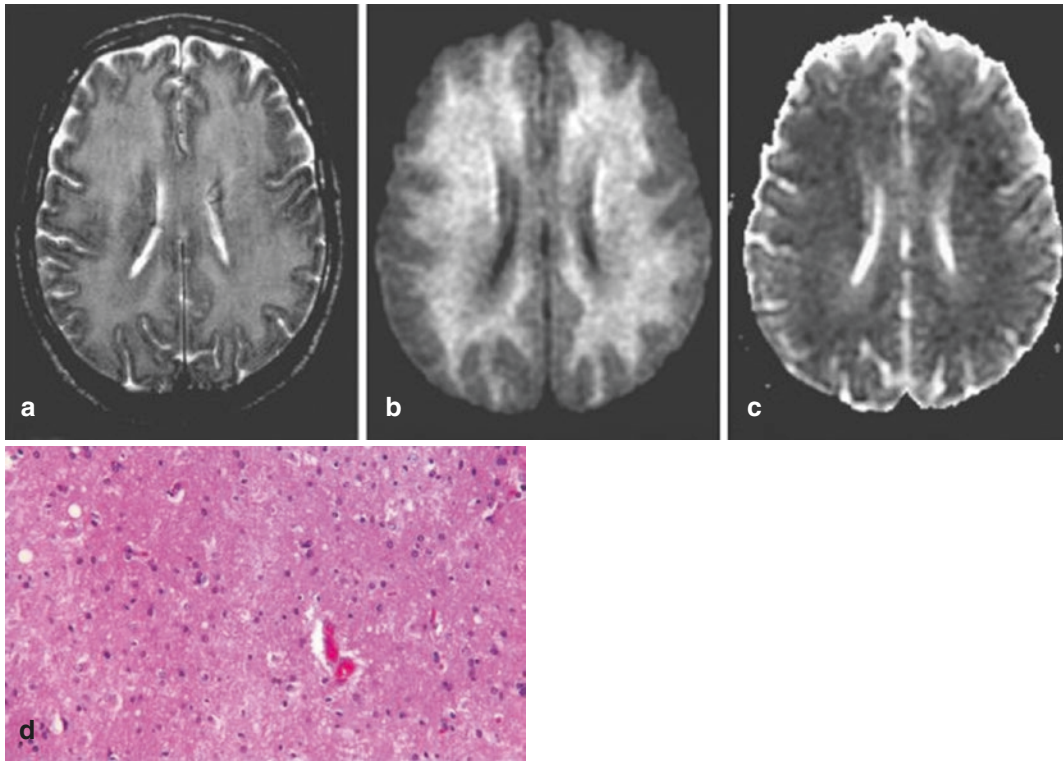


Fig. 15.5 Heroin-induced leukoencephalopathy in a 55-year-old man. (**a**) T2-weighted image shows diffuse hyperintensity in the white matter including U fibers. (**b**, **c**) DWI image shows these lesions as diffusely hyperintense with mildly decreased ADC. (**d**) Pathology shows intramyelinic edema and reactive astrogliosis, consistent with the subacute phase of heroin-induced leukoencephalopathy (hematoxylin–eosin stain, original magnification ×200)

have been variable. DWI showed increased ADC value consistent with vasogenic edema in lesions of the midbrain, pons, medulla, and cerebellar dentate nuclei, which involve mainly gray matter, but decreased ADC values indicating cytotoxic edema in lesions of the corpus callosum [34]. Improvement in clinical symptoms and imaging findings after discontinuation of metronidazole is noticed in the majority of cases; however, reversibility is not universal [33, 35].

15.1.6 Marchiafava–Bignami Disease

Marchiafava–Bignami disease is a rare complication of chronic alcoholism characterized by demyelination of the corpus callosum [36]. The genu of the corpus callosum is more frequently involved, but the degeneration can extend throughout the entire corpus callosum. Occasionally, optic chiasm and the visual tracts, putamen, anterior commissure, cerebellar peduncles, cortical gray matter, and U fibers may be involved. Clinical signs include seizures, impairment of consciousness, and signs of interhemispheric disconnection, but they are nonspecific.

The corpus callosum appears hypodense on CT and hyperintense on T2-weighted and FLAIR MR images, which is essential to confirm the diagnosis. These lesions can be partially reversible with treatment [37]. DW imaging shows lesions in the early phase as hyperintense with decreased ADC [38] representing cytotoxic edema, mainly in the myelin sheaths (intramyelinic edema). In the subacute phase, the lesions are hyperintense on DW imaging with increased ADC representing demyelination or necrosis (Fig. 15.8). DTI demonstrates reduced FA in the corpus callosum, and fiber-tracking demonstrates disruption of axonal

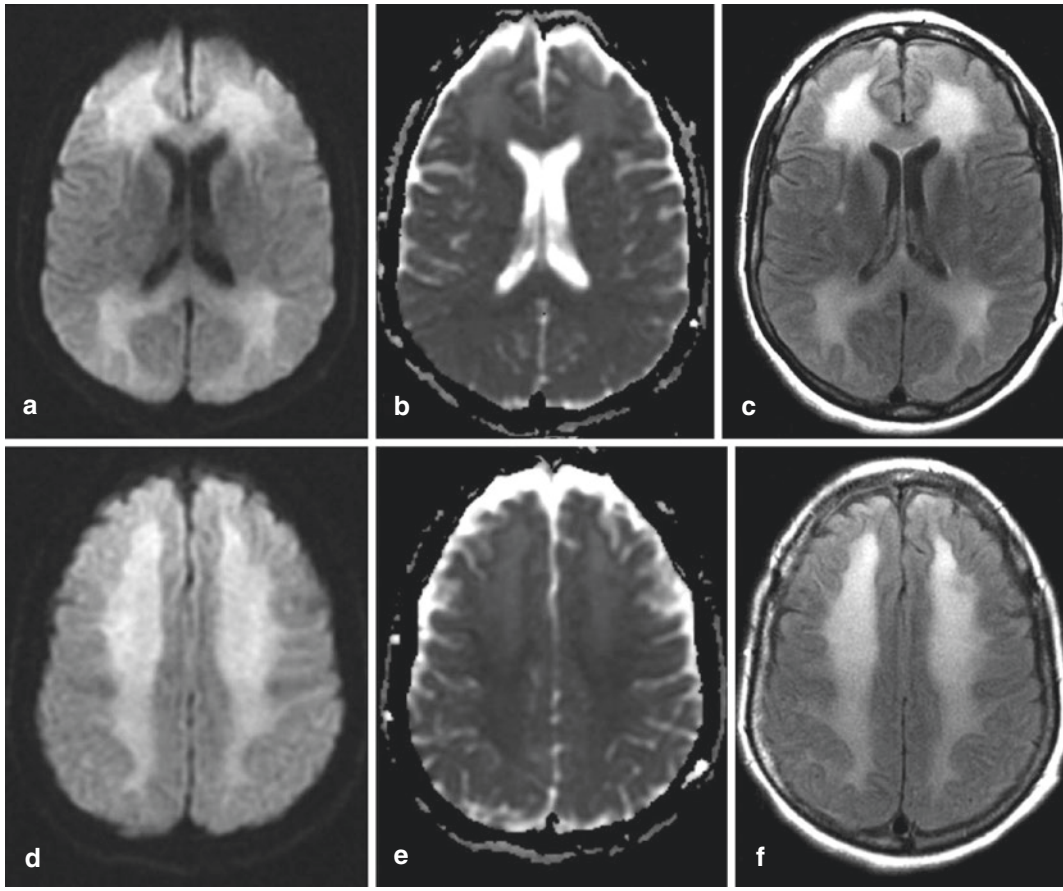


Fig. 15.6 49-year-old female with acute encephalopathy and positive urine screening for methadone. She had clinical recovery with no imaging follow-up (**a**, **d**: DWI, **b**, **e**: ADC map, **c**, **e**: FLAIR). Note simultaneous occurrence of facilitated diffusion anteriorly and restricted diffusion posteriorly in the ADC map

fiber bundles, most marked within the body of the corpus callosum [39]. The prognosis of Marchiafava–Bignami disease may be good even in cases with severe diffusion restriction of the entire corpus callosum if treatment with parenteral thiamine is initiated early, leading to imaging and clinical reversibility [40, 41].

15.2 Metabolic Diseases

15.2.1 Hypoxic–Ischemic Encephalopathy

Hypoxic-ischemic encephalopathy (HIE) is the result of decreased global perfusion or oxygenation. The distribution of HIE varies according to the duration, degree, and abruptness of the hypoxic and/or ischemic insults, basal blood flow, and metabolic activity in the areas of ischemia, temperature, and serum glucose levels [42, 43]. Hypoxia basically causes cardiac decompensation within minutes, resulting in global hypoperfusion and ischemic brain injury. However, pure anoxic encephalopathy may exist in some patients who are found early after the insult or who have suffered less severe anoxia [44]. In pure anoxia, cerebral blood flow is preserved allowing effective supply of nutrients and removal of toxic products such as lactic acid. Neurons tolerate pure anoxia for a longer duration than ischemia. Coma and other clinical findings can result from synaptic dysfunction.

DW imaging often depicts acute or subacute ischemic lesions when conventional MR imaging

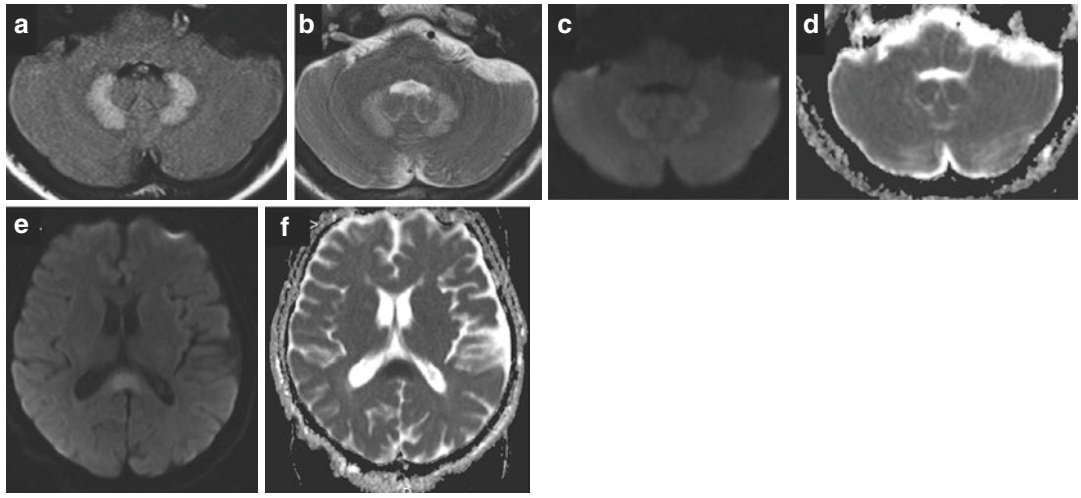


Fig. 15.7 69-year-old male with history of perforated appendix with phlegmon as well as pneumonia who has been on more than 2 months of metronidazole and moxfloxacin. He presented with 2–3 weeks of paresthesias in the bilateral feet, fall within the previous week with contusion to the head, dysarthria, and dysmetria for the past 3 days. FLAIR (**a**), T2-weighted (**b**), DWI (**c**), and ADC map (**d**) showing symmetric hyperintense lesions of the dentate nuclei. Additionally, there was a splenial lesion with restricted diffusion (**e**–**f**). (Courtesy Dr. Atsuhiko Handa, MD, University of Iowa Hospitals & Clinics)

and CT scans show only subtle abnormalities [45]. Layers 3 and 5 of the cerebral cortex, the CA1 field of the hippocampus, Purkinje neurons of the cerebellar cortex, and the watershed zones are most sensitive to ischemia [46]. Cortical laminar necrosis is observed as hyperintensity on T2-weighted, FLAIR images (variably seen as early as 1 day after injury) and on T1-weighted images from the subacute to chronic phase of HIE. DW imaging often depicts acute or subacute ischemic lesions when other MR sequences, and CT scans are still normal or show only subtle abnormalities [45]. DW hyperintensity throughout the cerebral cortex suggests devastating diffuse hypoxic-ischemic necrosis, whereas a pattern of basal ganglia or thalamic hyperintensity suggests primary hypoxic injury or mild HIE (Figs. 15.9 and 15.10). The prognosis of HIE depends on the extension of the cytotoxic edema, which is usually irreversible. DW imaging is helpful in establishing both the diagnosis and prognosis, and also in the management of HIE [47, 48]. High-*b*-value (3000 s/mm^2) DW imaging with long TE improves accuracy in the early detection of the HIE lesions [49].

15.2.2 Delayed Postanoxic Encephalopathy

Delayed postanoxic encephalopathy is a condition in which patients appear to make a complete clinical recovery after an episode of anoxia or hypoxia and then develop progressive neuropsychiatric symptoms and/or neurological deficits [50]. The incidence has been reported to range from 1 to 28 per 1000 suffering from hypoxic or anoxic events. It is most commonly associated with CO poisoning [51], but has also been reported after hypoxic events related to childbirth, surgery and anesthesia, drug overdose, exposure to toxins, anaphylaxis, seizures, cyanosis, and strangulation [52, 53]. The prognosis is variable from a full recovery to permanent neurologic sequelae, personality changes, and death. The pathogenesis is presumably related to programmed cell death/apoptosis of the oligodendrocytes triggered by hypoxia.

DW imaging shows diffuse hyperintensity with decreased ADC in the periventricular white matter and centrum semiovale, pathologically

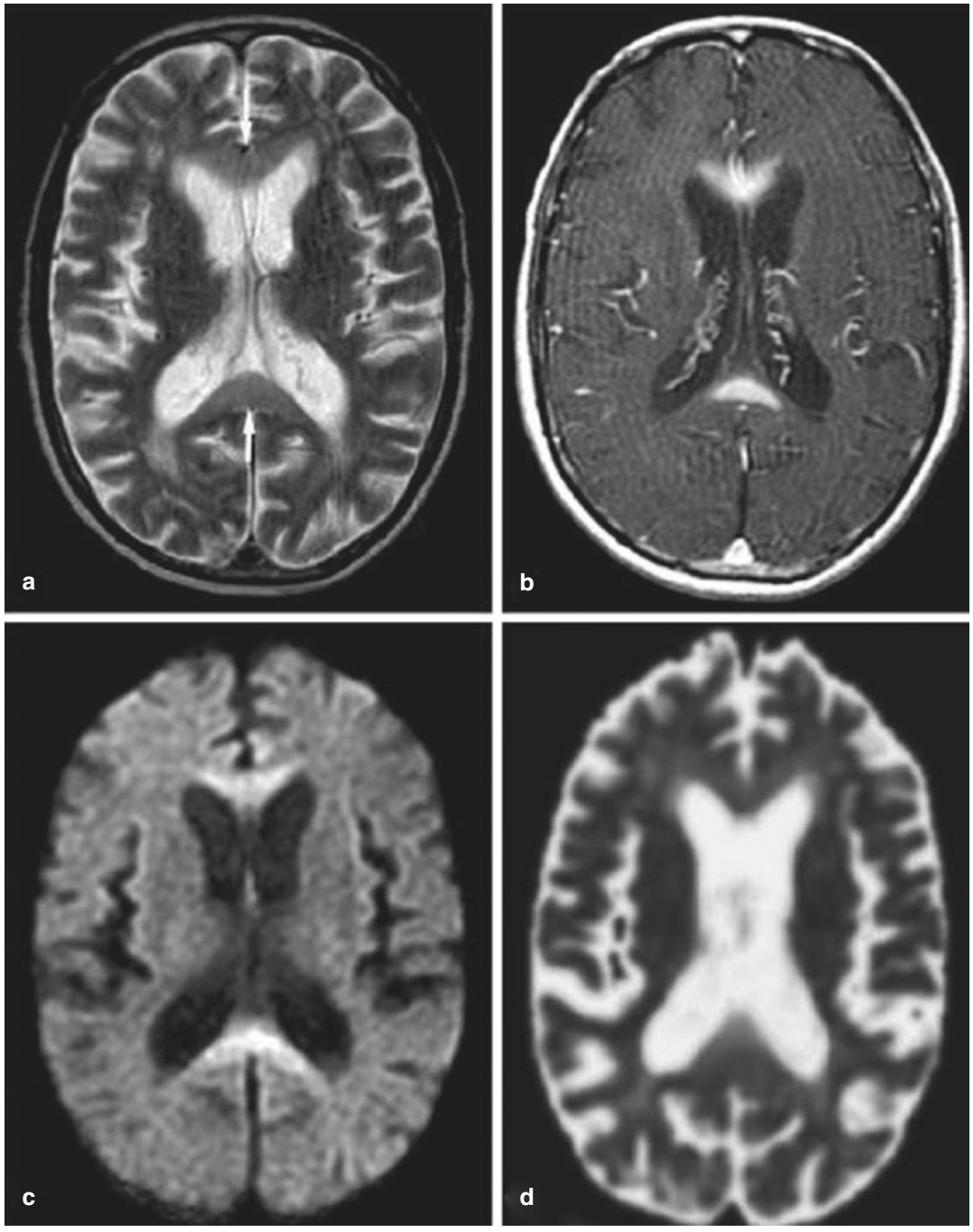


Fig. 15.8 Marchiafava–Bignami disease in a 58-year-old man. (**a**) T2-weighted image shows hyperintensity in the anterior and posterior corpus callosum (*arrows*) and in the periventricular white matter. (**b**) Gadolinium-enhanced T1-weighted image with magnetization transfer contrast reveals enhancing lesions in the anterior and posterior corpus callosum. (**c**, **d**) DW image shows hyperintense lesions with increased ADC in the corpus callosum, representing demyelination and necrosis in the subacute phase

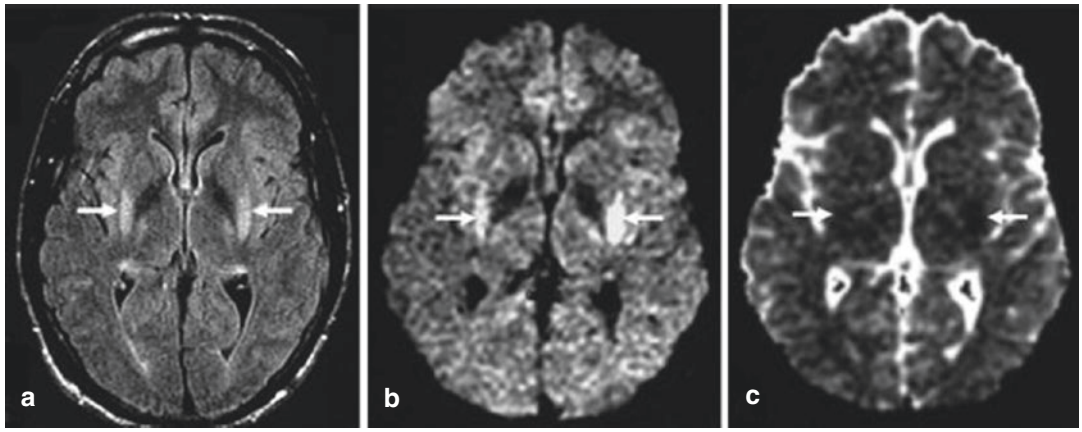


Fig. 15.9 Hypoxic-ischemic encephalopathy in an 18-year-old male patient after hanging himself. (**a**) FLAIR image shows hyperintensity in the posterior part of the putamina bilaterally. (**b**, **c**) DW image shows these lesions as hyperintense with the decreased ADC

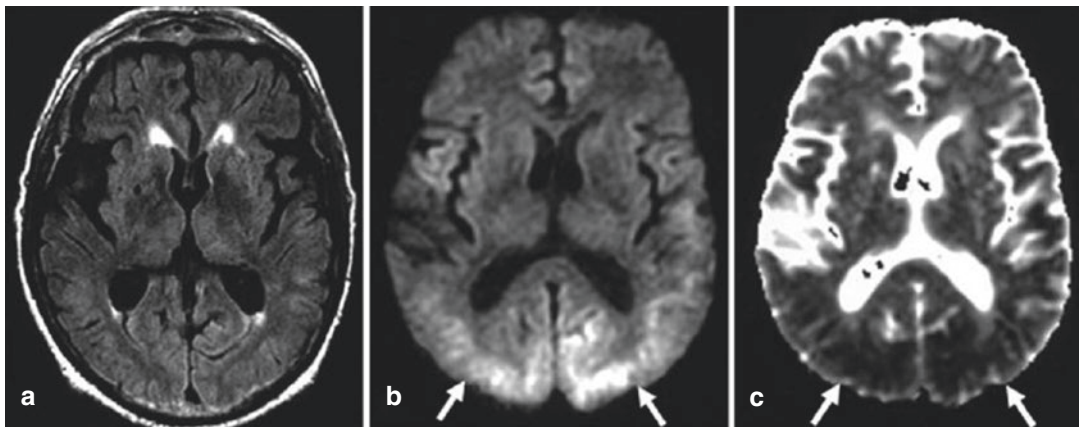


Fig. 15.10 Hypoxic-ischemic encephalopathy in an 83-year-old man with a cardiac arrest. (**a**) No obvious abnormality seen on FLAIR. (**b**, **c**) DW image shows extensive diffuse hyperintense lesions in the temporo-occipital cortices bilaterally (*arrows*) with decreased ADC values

consistent with cytotoxic edema in the myelin sheath (intramyelinic edema) (Fig. 15.11).

15.2.3 Brain Death

Brain death is defined as the irreversible cessation of all brain function [54]. Brain death criteria that most countries have commonly accepted are [55]: deep unresponsive coma; absence of brain stem function and reflexes; positive apnea test despite pCO_2 greater than 60 mmHg. The irreversibility of such criteria must be confirmed. Brain electrical activity (EEG, brain stem evoked potentials) may be inaccurate in comatose patients with drug-induced hypothermia or intoxication. The absence of cerebral blood flow is accepted as a confirmatory sign of brain death.

Conventional angiography was considered the gold standard until the 1990s, but it is an invasive method and may damage transplantable organs. MR imaging and MR angiography have been

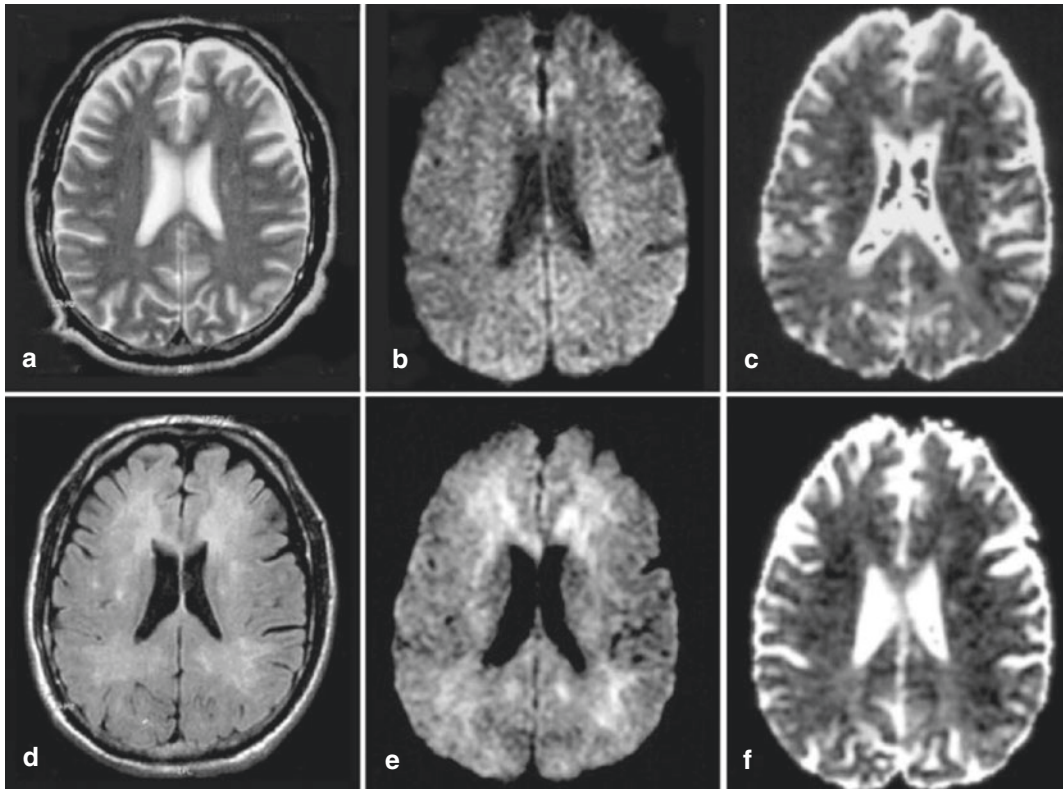


Fig. 15.11 Delayed postanoxic encephalopathy in a 53-year-old man with progressive mental status changes for 3–4 days. There was a history of narcotic overdose 2 weeks earlier. (**a**) T2-weighted image shows no abnormal signal intensity in the brain. (**b**, **c**) DW image shows very subtle hyperintensity with mild decreased ADC in the corona radiata. (**d**) Follow-up MR imaging was performed 14 days after the onset. FLAIR image shows high signal intensity in the deep white matter bilaterally. (**e**) DW images revealed diffuse hyperintensity with decreased ADC (**f**). The patient continued to deteriorate and died about 20 days later, 46 days after the overdose. Autopsy was performed. (**g**–**i**) Pathology shows myelin discoloration in the periventricular white matter and caudate nucleus. Pathology shows neuronal axonal spheroids (*arrows*) in the gray matter **(h)** and varying degrees of myelin loss with spongiform changes in the white matter, reflecting intramyelinic edema in the deep white matter (**i**)

reported as reliable methods in demonstrating absence of cerebral blood flow and determining brain death [54, 56, 57]. MR findings in brain death include (1) central and tonsillar herniation, (2) absent intracranial vascular flow voids, (3) poor gray matter/white matter differentiation, (4) no intracranial contrast enhancement, (5) carotid artery gadolinium enhancement (intravascular enhancement sign), and (6) prominent nasal and scalp enhancement (MR hot nose sign) [56]. MR angiogram shows no intracranial flow above the supra-clinoid carotid arteries due to the increased intracranial pressure. DW imaging shows diffuse hyperintense areas in the gray and white matter including the brain stem (Figs. 15.12 and 15.13). A massive drop in ADC values in the hemispheres has been reported (<50% of normal values) [58]. The ADC value of the white matter is significantly lower than that of the gray matter [59]. Diffusion restriction usually extends to the brain stem and, variably, the cerebellum [60]. Severe ADC reduction in gray and white matter probably reflects global irreversible cytotoxic edema.

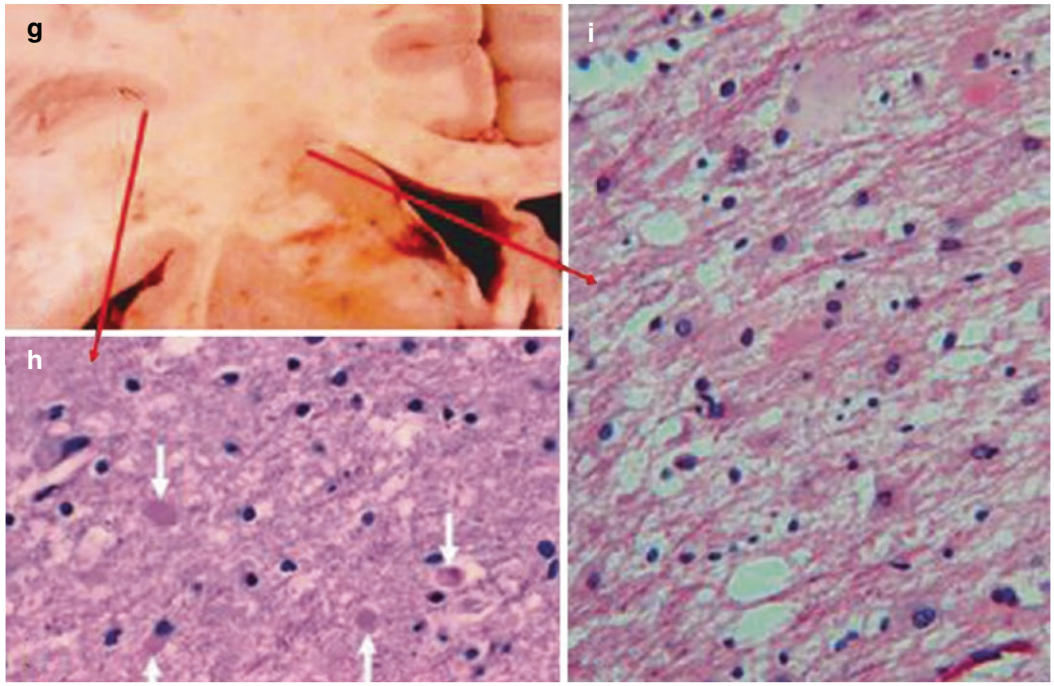


Fig. 15.11 (continued)

15.2.4 Hypoglycemia and Hyperglycemia

Glucose is the main energy substrate of the brain. Hypoglycemia is caused by overuse of insulin, oral hypoglycemic agents, insulinoma, sepsis, renal or hepatic failure, or Addison disease. Neurologic signs of hypoglycemia are nonspecific including weakness, confusion, seizures, and coma. Sequelae of hypoglycemic coma are rare, but they include profound memory loss, persistent vegetative state, and death in 2–4% of cases. MR imaging of hypoglycemia shows lesions that involve the cerebral cortex, particularly the temporal lobe, hippocampus, and basal ganglia [61]. The most severely affected patients manifest basal ganglia involvement. DW imaging shows hyperintense lesions with decreased ADC similar to hypoxic–ischemic encephalopathy (Fig. 15.14) [61, 62]. Reversible lesions on DW imaging have also been reported, which often involve the bilateral internal capsules, corona radiata, and corpus callosum [63, 64]. This pattern may be the result of a different pathophysiologic process from glucose starvation such as a release of excitatory amino acids into the extracellular space [65].

Hyperglycemia can disrupt the blood–brain barrier and produce decreased cerebral blood flow, intracellular acidosis, accumulation of extracellular glutamate, and decreased activity of GABAergic neurons. Hemichorea-hemiballismus associated with hyperglycemia is characterized by hyperintensities in the striatum on T1-weighted images and CT studies. The process is either unilateral or bilateral. The T1 high signal is probably related to manganese (Mn) accumulation accompanied by induction of Mn superoxide dismutase (MN-SOD) and glutamine synthetase (GS) with rich protein contents in the reactive swollen astrocytes (gemistocytes) [66–68]. Increased viscosity was also proposed as a potential basis for the high T1 signal, which could also explain restricted diffusion [67]. DW imaging has been

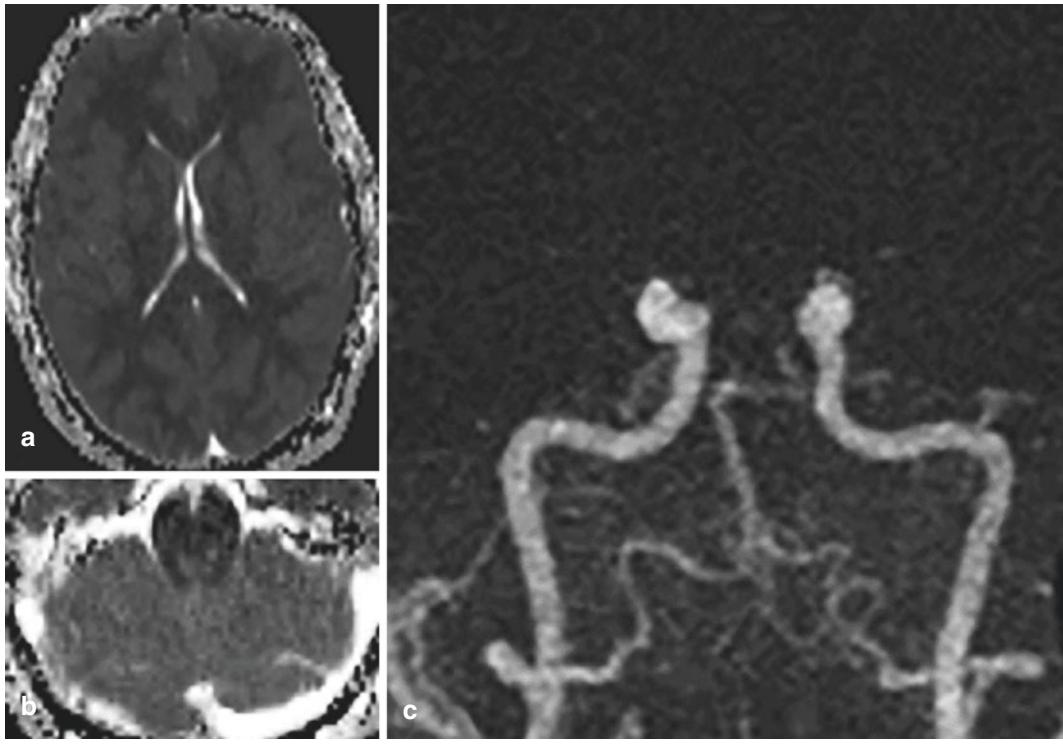


Fig. 15.12 32-year-old man with brain death. (**a**) ADC map reveals marked decreased ADC in the white matter (0.21×10^{-3} mm^2/s) and decreased ADC in the cortex (0.51×10^{-3} mm^2/s). Note diffuse obliteration of cortical sulci. (**b**) Decreased ADC is observed in the pons (0.30×10^{-5} mm^2/s) but not in the cerebellum. (**c**) Dynamic contrast MR angiography shows loss of vascular flow in the supraclinoid internal carotid arteries but reveals opacification of intracranial vertebral and basilar arteries

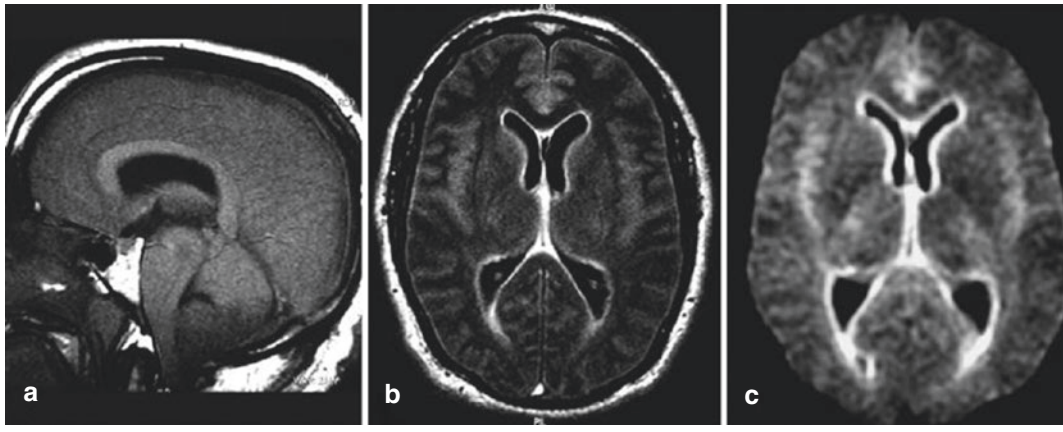
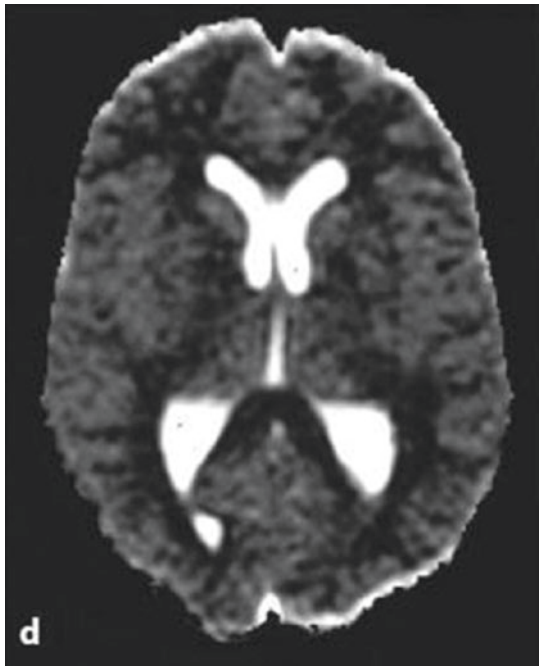
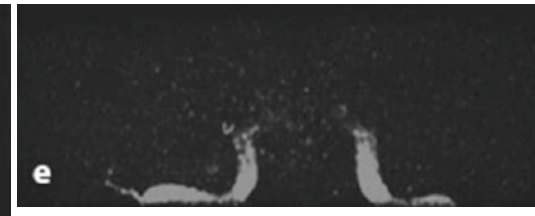


Fig. 15.13 Brain death in a 48-year-old man. (**a**) Sagittal T1-weighted image shows central and tonsillar herniation. (**b**) FLAIR image shows diffuse hyperintensity in the cortex, deep gray matter, and periventricular white matter. (**c**) DW image shows extensive diffuse hyperintensity in the brain, especially the periventricular white matter. (**d**) The ADC values of the brain are diffusely decreased in the cortex (0.51×10^{-3} mm^2/s) and white matter (0.25×10^{-3} mm^2/s). (**e**) MR angiography shows nonvisualization of intracranial vessels above the supraclinoid carotid arteries





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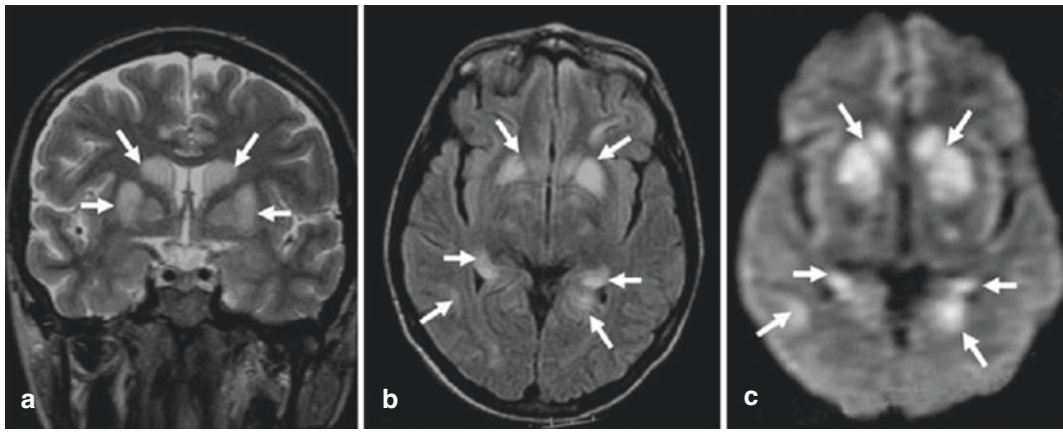

Fig. 15.14 Hypoglycemic encephalopathy in a 53-year-old man. (**a**, **b**) Coronal T2-weighted and axial FLAIR images show symmetric hyperintense lesions in the basal ganglia, hippocampi, and temporo-occipital lobes (*arrows*). (**c**) DW image shows these areas as hyperintensity lesions (*arrows*)

reported to detect early ischemic damage as areas of heterogeneous signal intensity with decreased ADC (Fig. 15.15) [67–69]. On the other hand, diabetic ketoacidosis with prolonged hyperglycemia may cause subtle FLAIR and diffusion abnormalities in the cortex (Fig. 15.16) associated with elevations in glucose, myoinositol, taurine, and ketones in MR spectroscopy [70].

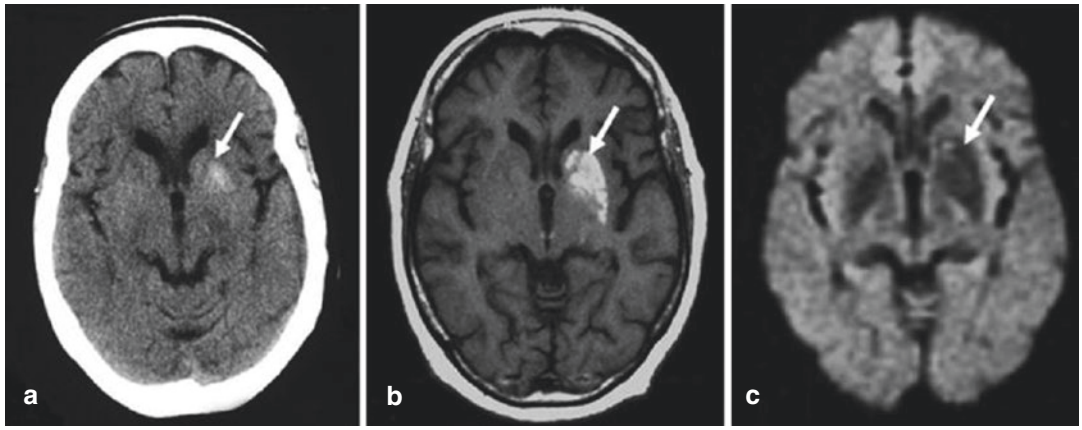

Fig. 15.15 Hemichorea-hemiballismus associated with hyperglycemia in a 69-year-old woman with type 2 diabetes. (**a**) CT shows high-density areas in the left caudate head and anterior part of the putamen (*arrow*). (**b**) T1-weighted image shows hyperintensity in the left entire striatum (*arrows*). (**c**) DW image shows these lesions as low-signal intensity with an isointense area in the left caudate head (*arrows*)

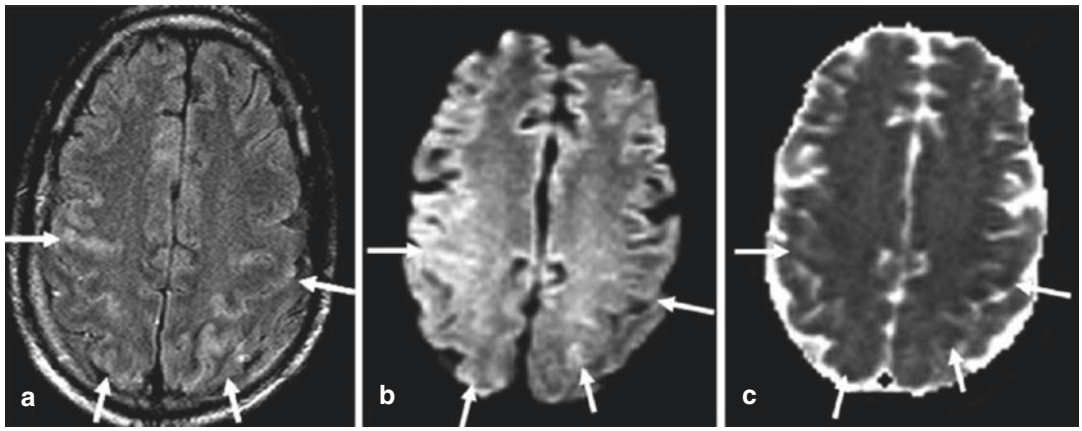

Fig. 15.16 Diabetic ketoacidosis with type 1 diabetes in a 28-year-old man (blood sugar 1500 mg/dl). (**a**) FLAIR image shows symmetric hyperintense lesions in the parietal cortices bilaterally. (**b**, **c**) DW image shows these areas as hyperintense with mildly decreased ADC

15.2.5 Osmotic Demyelination (OD)

OD encompasses previously reported central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM), which represent destruction of myelin sheaths in characteristic locations within the brain stem and cerebrum. The most common location is the central part of the basis pontis, followed by a combined type with central and extrapontine areas of myelinolysis. Isolated EPM is the least common presentation [71]. A symmetric trident-shaped hyperintensity in the central pons is the characteristic finding on T2-weighted and FLAIR MR images. The ventrolateral pons and the corticospinal tracts typically are spared [72]. The basal ganglia, thalamus, geniculate bodies, internal and external capsules, corpus callosum, cerebellum, cerebellar peduncles, and gray–white matter junction are possible sites of EPM [73–76]. The cortico-subcortical junction, especially at the crown of the cortical gyri, is vulnerable to osmotic demyelination syndrome [77, 78]. The synonyms

include osmotic myelinolysis and osmotic demyelination syndrome. Symptoms include acute confusional state, pseudobulbar affect, stupor, coma, and occasionally locked-in syndrome, intermingled with prominent motor manifestations of flaccid evolving to spastic quadriparesis, dysarthria, and dysphagia [79–81].

Pathological findings show destruction of myelin sheaths, though the nerve cells and axons are relatively spared. The underlying etiology and pathogenesis are unknown, but the hypotheses include osmotic endothelial injury, microglia-derived cytokines, excessive brain dehydration, and metabolic compromise [82]. Organic osmolytes, including glutamate, glutamine, myoinositol, and taurine, have been implicated in the pathogenesis of myelinolysis [83]. The most common osmotic insult is a rapid correction of compensated subacute hyponatremia. However, CPM and EPM can also occur in normo- or hypernatremic states in patients with chronic alcoholism, post-liver transplantation, malnutrition, burns, hyperemesis gravidarum, and AIDS [84–86].

MR imaging has a fundamental role in the diagnosis and discloses hyperintense lesions on T2-weighted images, with or without enhancement on gadolinium-enhanced T1-weighted images. DW imaging is useful in detecting the lesions in the early phase as hyperintense with decreased ADC, which represents cytotoxic edema (Figs. 15.17, 15.18, and 15.19) [87]. Cytotoxic edema in CPM and EPM occur not only in myelin sheaths but also in neurons, axons, and astrocytes [88]. The clinical outcome of CPM and EPM is highly variable, and both fatal and clinically reversible cases may be associated with this kind of cytotoxic edema.

15.2.6 Wernicke's Encephalopathy

Thiamine (vitamin B1) deficiency can cause Wernicke encephalopathy, characterized by confusion, ataxia, and abnormal eye movements, but the classical clinical triad is not always present. It is frequently associated with chronic alcohol abuse. Nonalcoholic Wernicke encephalopathy includes many other conditions such as tumors and bypass surgery of the gastrointestinal tract, gastroplasty, pancreatitis, anorexia nervosa, voluntary food starvation, hyperemesis gravidarum, chronic uremia, dialysis, HIV infection, and thyrotoxicosis [89–91]. Without thiamine, the Krebs and pentose phosphate cycles cannot metabolize glucose. Thiamine is also essential in maintaining osmotic gradients across cell membranes. Cellular homeostasis will soon fail resulting in release of glutamate into the extracellular space leading to NMDA receptor mediated excitotoxicity. Pathologic features are edema, swelling of capillary endothelial cells and astrocytes, hemorrhage, necrosis, and decreased myelination. The lesions are commonly seen in the mamillary bodies (57–75%), medial thalamic and hypothalamic nuclei, periaqueductal

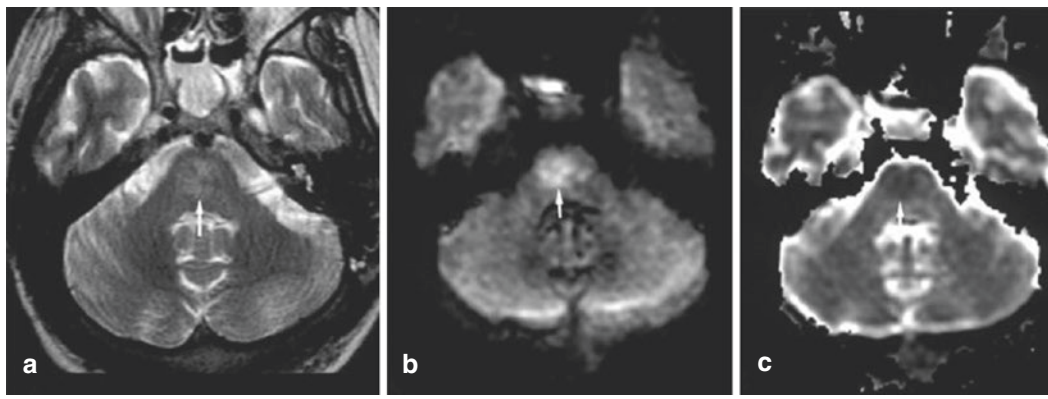

Fig. 15.17 Central pontine myelinolysis in a 33-year-old man. (**a**) T2-weighted image shows a hyperintense lesion in the center of the pons (*arrow*). (**b**, **c**) DW image shows this lesion as hyperintense with decreased ADC

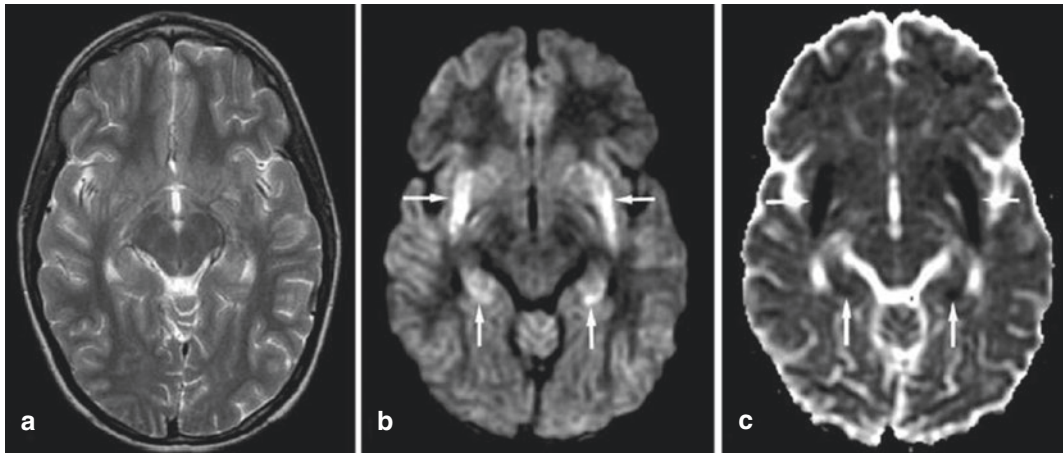

Fig. 15.18 Extrapontine myelinolysis in an 11-year-old boy. (**a**) T2-weighted image shows no appreciable abnormality in the external capsules and hippocampi. (**b**, **c**) DW image demonstrates bilateral symmetrical hyperintense lesions with decreased ADC in the external capsules and hippocampi (*arrows*), representing cytotoxic edema

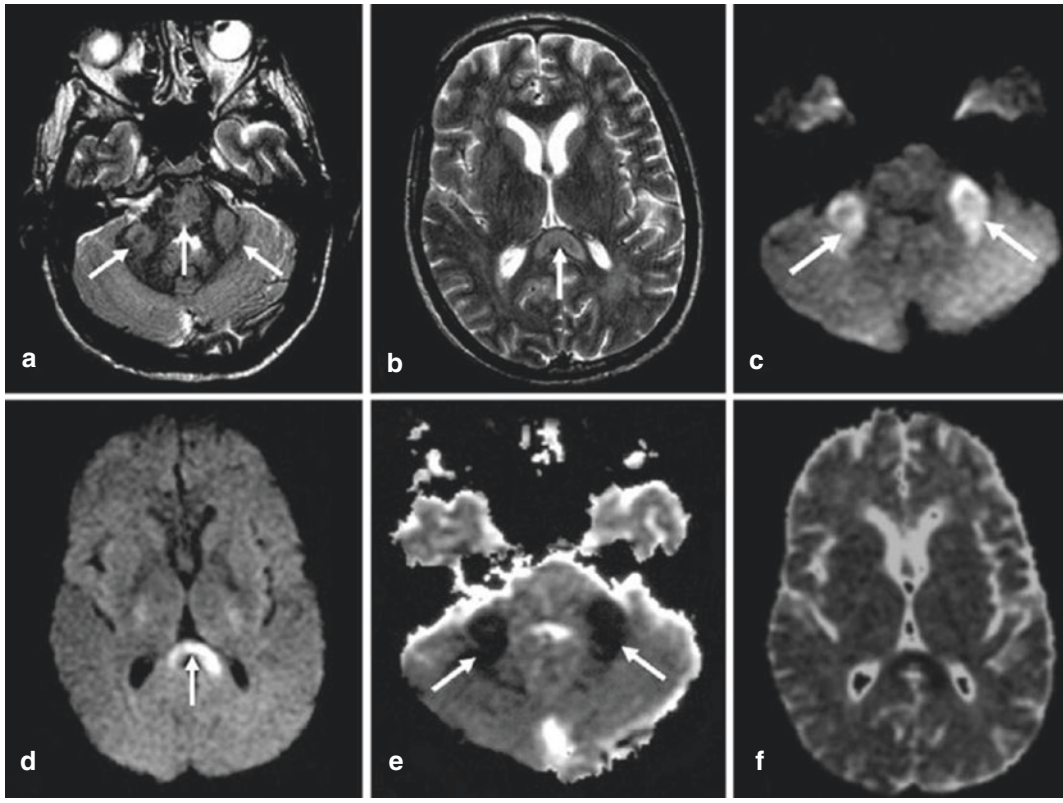

Fig. 15.19 Central pontine and cerebellar peduncle myelinolysis in a 54-year-old man with slurred speech and confusion. (**a**, **b**) T2-weighted image shows hyperintense lesions in the center of the pons, middle cerebellar peduncles (**a**), and corpus callosum. (**b**) (*arrows*). (**c**–**f**) DW image shows the lesions in the middle cerebellar peduncles and corpus callosum as hyperintense with decreased ADC (*arrows*), and the pontine lesion as isointense with increased ADC

gray matter, tectal plate, walls of the third and floor of the fourth ventricle, and less commonly in the caudate nuclei, frontal, and parietal cortex, pons, dorsal medulla, red nuclei, corpus callosum, cerebellum, and dentate nuclei [91–95].

MR imaging shows symmetrical hyperintense lesions of these areas on FLAIR and T2-weighted images [96]. They may or may not show enhancement on T1weighted images following contrast agent injection, depending on local disruption of the blood–brain barrier [91, 97]. Mammillary body involvement and enhancement are often seen in Wernicke encephalopathy with alcohol abuse but are less frequent in nonalcoholic Wernicke encephalopathy [89–91]. With intravenous thiamine treatment, these lesions may resolve. DW imaging shows these lesions as hyperintense with decreased or increased ADC. Lesions with decreased ADC are thought to represent cytotoxic edema of neurons or astrocytes, while lesions with increased ADC may represent vasogenic edema (Figs. 15.20 and 15.21) [95, 98–100]. Both types of lesion can be reversible [98]. The important differential diagnosis of symmetric lesions in the medial thalami includes ischemia due to occlusion of the artery of Percheron and deep cerebral vein thrombosis.

15.2.7 Hyperammonemic Encephalopathy

Hyperammonemia is the end result of several metabolic derangements such as hepatic encephalopathy, deficiencies of urea cycle enzymes, Reye's syndrome, and other toxic encephalopathies [102]. FLAIR and DWI display abnormalities in the thalami, posterior limb of the internal capsule, periventricular white matter, dorsal brainstem, or diffuse cortical involvement. Restricted diffusion involving the insular and cingulate cortices and thalamus bilaterally is characteristic (Fig. 15.22) [103]. FLAIR and DWI changes correlate with plasma ammonia level, which is a strong predictor of outcome [104]. The combination of facilitated and restricted diffusion suggests the presence of both intracellular and extracellular components of cerebral edema in patients with acute-on-chronic liver failure [105]. The time course of ADC changes is reminiscent of HIE, with pseudonormalization at 8 days [101]. In well-compensated cirrhosis patients free of overt hepatic encephalopathy, ADC values were significantly increased in the genu and body of the corpus callosum suggesting increase in extracellular fluid [106].

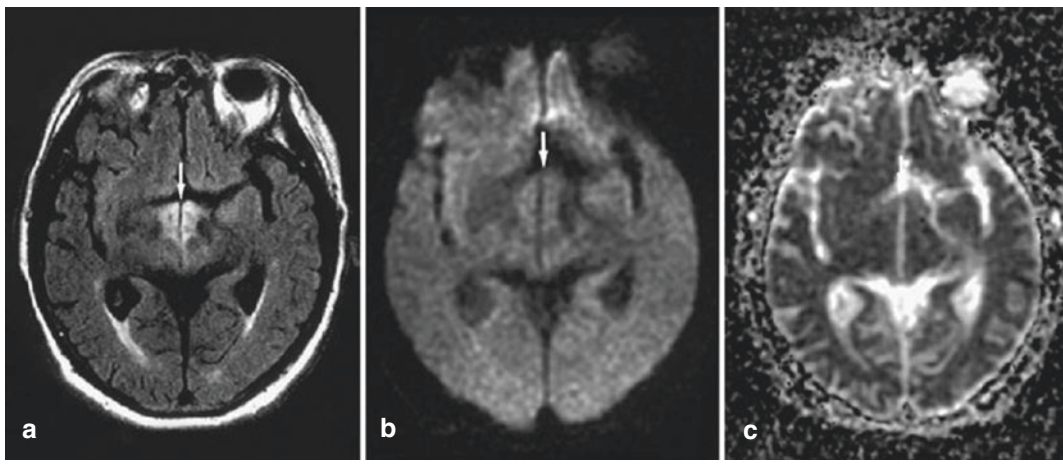

Fig. 15.20 Wernicke encephalopathy with alcohol abuse in a 75-year-old man. (**a**) FLAIR shows a symmetrical hyperintense lesion in the hypothalamus (*arrow*). (**b**, **c**) DW image shows isointense lesions with increased ADC in the hypothalamus, which may represent vasogenic edema (*arrow*)

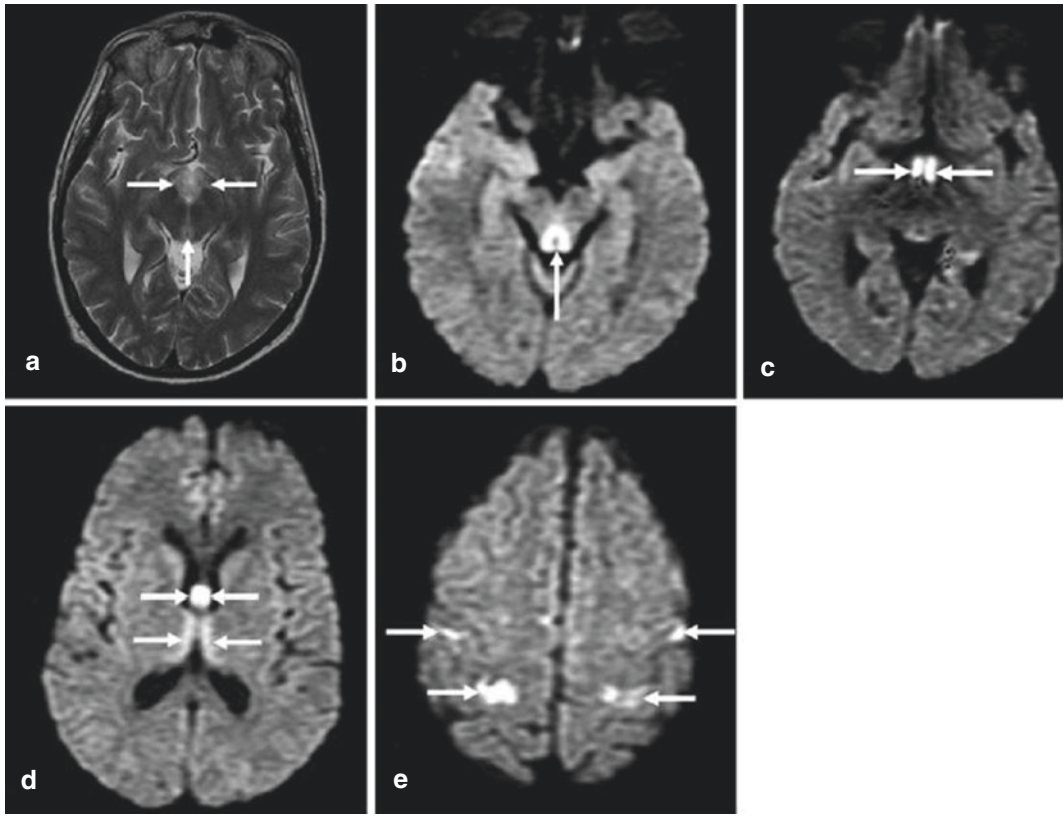

Fig. 15.21 Wernicke encephalopathy with thyrotoxicosis in a 36-year-old man. (**a**) T2-weighted image shows symmetric hyperintense lesions in the mammillary bodies, hypothalamus, and periaqueductal region (*arrows*). (**b**–**e**) DW imaging shows hyperintense lesions in the hypothalamus, midbrain tectum, periaqueductal region, medial thalami, fornices, and pre- and postcentral gyri (*arrows*), associated with partially decreased ADC (not shown)

15.2.8 Wilson's Disease (WD)

The incidence of WD is approximately 1:30,000. The underlying mechanism of WD is a defect in ATP7B, a copper transporting ATPase that is mainly expressed in hepatocytes. This leads to accumulation of copper, which eventually overwhelms safe storage capacity and cellular injury occurs. Most WD patients present with liver disease during their first and second decades of life with neurologic or psychiatric symptoms in the second and third decades or later on [107]. Neurologic disease most often presents with tremor and progresses with gait imbalance, dysarthria, drooling, and parkinsonism. Psychiatric disease may range from mild mood disturbance to frank psychosis.

On T2-weighted images, neurological WD patients show high signal changes in the putamen, followed by involvement of the caudate, midbrain, thalamus, and cerebral cortex (Fig. 15.23) [108, 109]. The appearance of axial T2-weighted images at the midbrain has been linked to a "giant panda" face sign [110]. On DWI images, restricted diffusion in the putamen can be detected before the occurrence of neurologic manifestations in WD. In contrast, an increase in diffusion is detected after the occurrence of symptoms within the putamen, pallidum, internal capsule, and subcortical white matter, which parallel the signal changes seen on FLAIR [111].

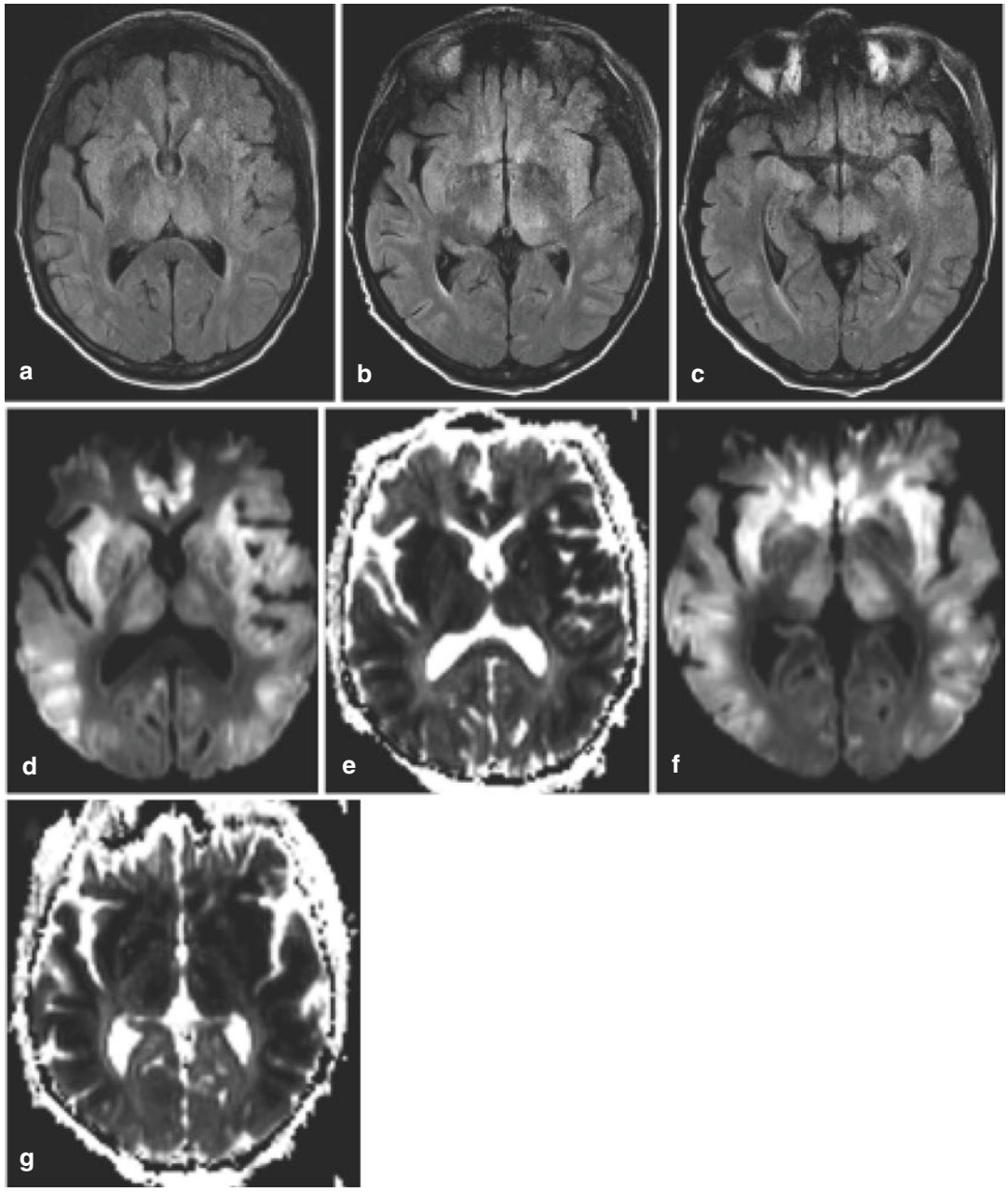

Fig. 15.22 Hyperammonemic encephalopathy in a 55-year-old man with cirrhosis, subsequently fatal, with initial plasma ammonia level (PAL) of 410 μM/L. (**a**–**c**) Axial FLAIR symmetric hyperintensities in thalami, upper midbrain, insula and external capsule and temporal cortex. DWI trace images (**d** and **f**) and ADC map (**e** and **g**) display extensive restricted DWI in those areas. The graph shows temporal evolution of ADC changes with pseudonormalization at 8 days [101]

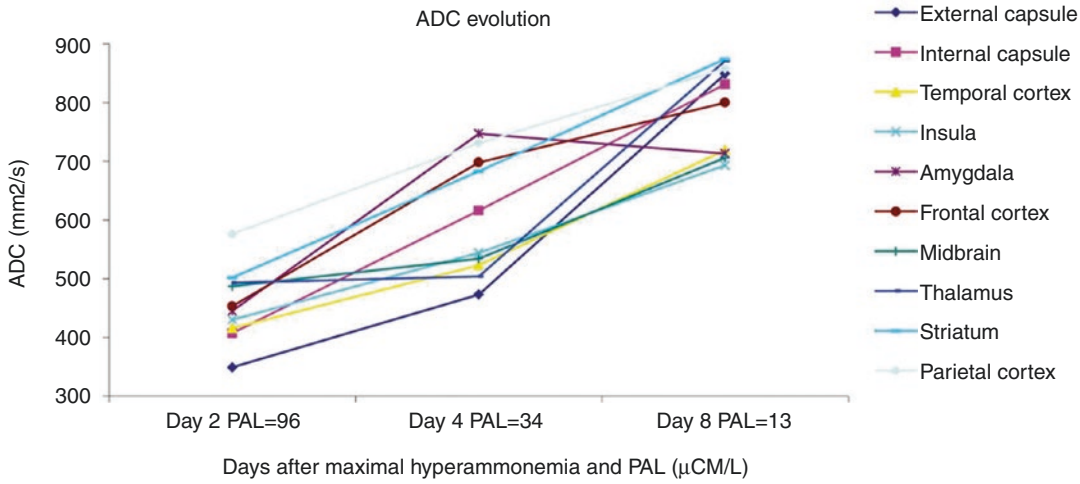

Fig. 15.22 (continued)

15.2.9 Mitochondrial Encephalopathies

Mitochondrial encephalopathies are a heterogeneous group of disorders affecting primarily the central nervous system and skeletal muscles that result from mutations in the mitochondrial DNA that are inherited through the maternal line. Two main hypotheses attempt to explain the cerebral lesions: (a) mitochondrial dysfunction, which results in anaerobic metabolism and neuronal death from acidosis and (b) metabolic damage of the endothelium, which leads to small-vessel occlusion and secondary neuronal death [112].

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is one of the most frequent mitochondrial disorders. MELAS syndrome is a multi-organ disease with stroke-like episodes, dementia, epilepsy, lactic acidemia, myopathy, recurrent headaches with vomiting, hearing impairment, diabetes, and short stature [112]. 80% of MELAS cases are associated with the m.3243A > G mutation in the MT-TL1 gene encoding the mitochondrial $tRNA^{Leu(UUR)}$ (Fig. 15.24). On the other hand, Leigh syndrome displays a wide variety of presentations, from severe neurologic symptoms to subtle abnormalities. Most frequently, the central nervous system is affected with psychomotor retardation, seizures, nystagmus, ophthalmoparesis, optic atrophy, ataxia, dystonia, or respiratory failure. Some patients also present with peripheral nervous system involvement, including polyneuropathy or myopathy, or non-neurologic abnormalities, e.g., diabetes, short stature, cardiomyopathy, anemia, renal failure, vomiting, or diarrhea (Leigh-like syndrome) [113]. Onset is in early childhood, but in a small number of cases, adults are affected (Fig. 15.25).

T2-weighted images occasionally show increased signal intensity in the cortex and subcortical white matter, with features reminiscent of stroke but not respecting vascular territories. Cerebellar atrophy may be a hint to a preexisting abnormality (Figs. 15.24 and 15.25). Proton MR spectroscopy is useful in the diagnosis by detecting elevated lactate peak. DW imaging often shows the stroke-like lesions in MELAS as hyperintense with restricted diffusion initially and later facilitated diffusion [114]. They have increased or normal ADC, which presumably represents vasogenic edema, however, decreased ADC in these lesions representing cytotoxic edema can be observed [114] (Fig. 15.25).

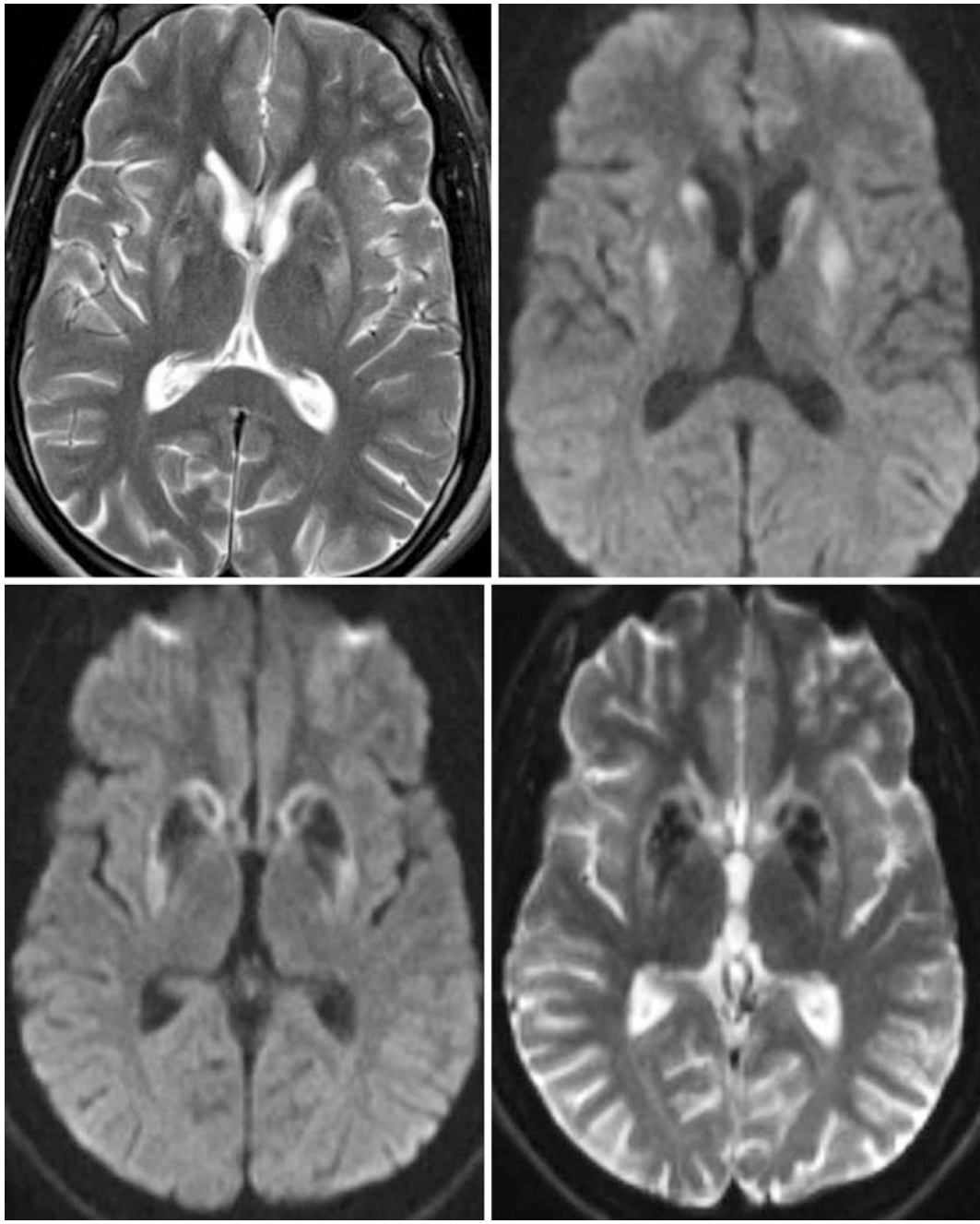

Fig. 15.23 **Wilson disease** 19 year/o male with slurred speech, change in behavior, depression, and low ceruloplasmin. Symmetric T2 and DWI hyperintensities with facilitated diffusion in the striatum

15.2.10 SMART Syndrome

SMART syndrome (stroke-like migraine attacks after radiation therapy) is a rare condition that involves complex migraines with focal neurologic findings in patients following cranial irradiation for central nervous system malignancies. It may be diagnosed up to 35 years (on average 20 years) after high-dose radiation (>5000 centi Gray) treatment for intracranial neoplasms. It

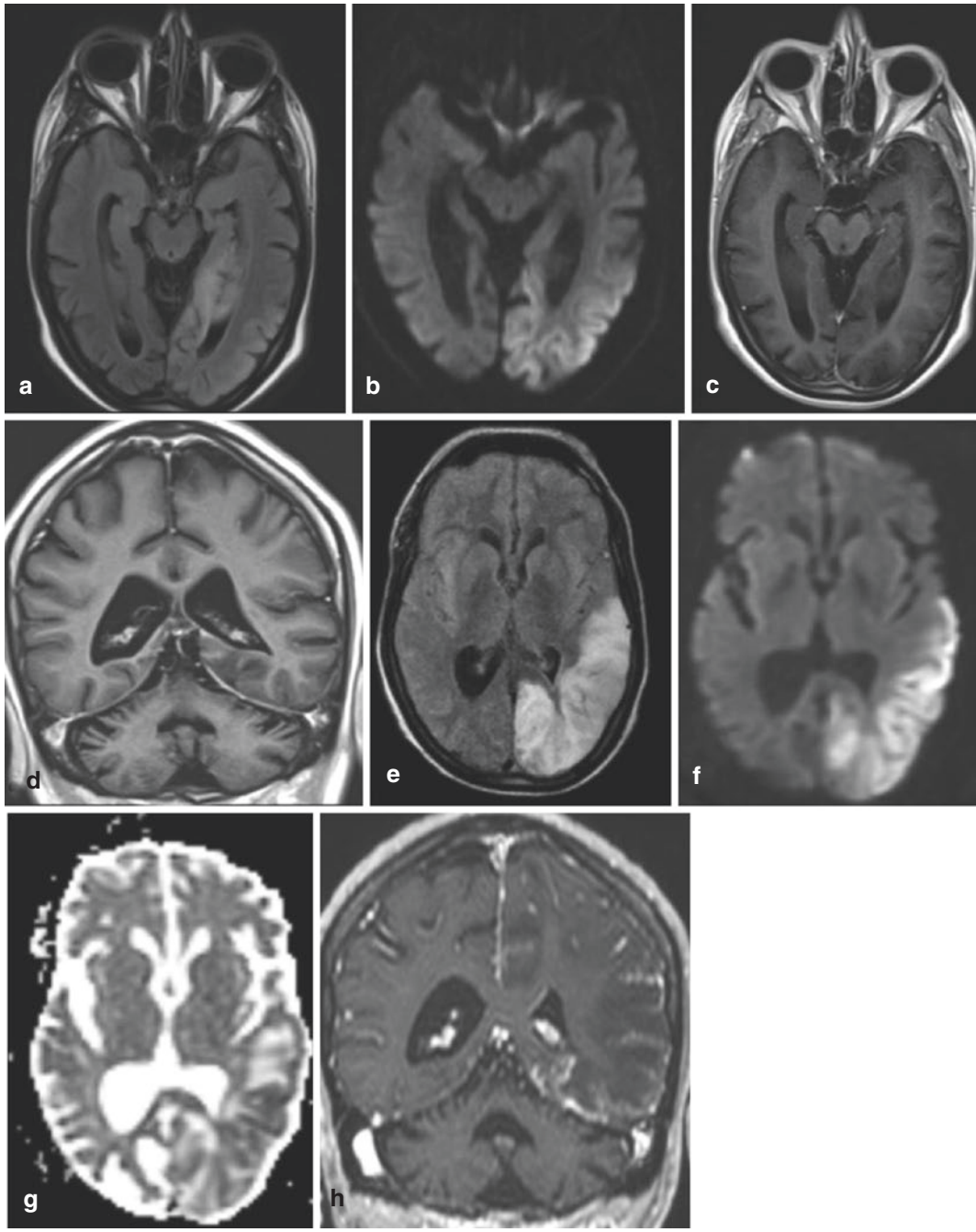

Fig. 15.24 **MELAS** 42-year-old female with headache, blurry vision, and altered mental status. Hereditary deafness in maternal line. m.3243A > G pathogenic variant in the MT-TL1 gene. (**a**–**d**) At presentation, (**e**–**h**) follow-up with worsening cortical-based restricted DWI (**f**–**g**), and cortical enhancement (**h**)

involves complicated migraine symptoms consisting of transient neurologic deficits such as hemiparesis, aphasia, and sensory disturbances [115]. On imaging, it may resemble subacute infarction or MELAS on post-contrast images (Fig. 15.26): unilateral gyriform enhancement on MR imaging that develops within 2–7 days and resolves in 2–5 weeks. On the other hand,

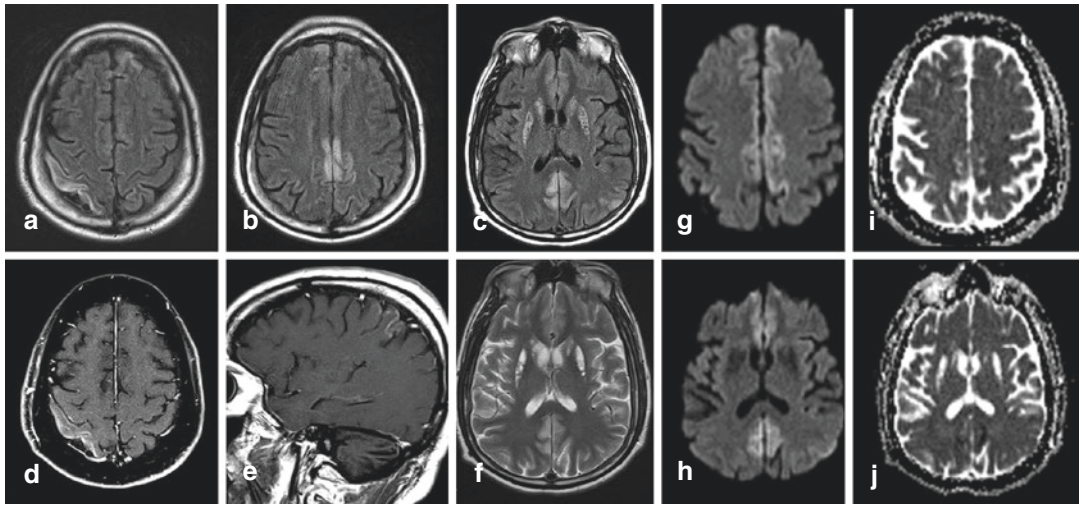

Fig. 15.25 **Adult Leigh syndrome**. 42-year-old man with a pathogenic mutation in MTATP6. Had recurrent stroke-like episodes, imaging evidence of necrotizing encephalopathy, decompensation at the time of infectious illness, chronic migraine, sensorineural hearing loss, and psychotic symptoms. Also had lifelong progressive muscle weakness, ataxia, cerebral and cerebellar atrophy, and visual problems. Symmetric gray matter symmetric involvement with high FLAIR signal in cortex and basal ganglia (**a**–**c**), with cortical enhancement (**d**–**e**) and restricted DWI (**g**–**j**). Note basal ganglia (**c**–**f**) and cerebellar (**e**) atrophy

DWI abnormalities primarily demonstrated T2 shine through without convincing evidence of restricted diffusion as opposed to mitochondrial diseases. Although considered reversible, up to 45% of SMART cases had incomplete neurologic recovery with imaging or clinical sequelae such as dysphasia, cognitive impairment, or hemiparesis [116].

15.3 Treatment of Toxic and Metabolic Diseases

Yang Mao-Draayer and Brian Chang

15.3.1 Chemotherapy-Induced Leukoencephalopathy

The most commonly implicated agent associated with leukoencephalopathy is methotrexate, and there is no standardized treatment for methotrexate-induced leukoencephalopathy [117]. Some case reports have suggested benefit with aminophylline and a retrospective series of patients with subacute encephalopathy found improvement with dextromethorphan [118, 119]. However, whether methotrexate in general should even be stopped should be assessed with relation to many mitigating factors, including determination of why the affected patient was more at risk for toxicity, whether leukoencephalopathy was symptomatic or not, how extensive the leukoencephalopathy was, and how much the patient would benefit from continuing methotrexate [120]. Other methotrexate-induced neurotoxicities—specifically transverse myelopathy and disseminated necrotizing leukoencephalopathy—require immediate discontinuation of methotrexate [121, 122]. A case report of the former has documented improvement with high doses of metabolites of the methyl-transfer pathway including S-adenosylmethionine, folinate, cyanocobalamin, and methionine [123]. The latter has been associated with poor outcomes, with supportive treatment as the only therapeutic management [2].

While less common, other chemotherapies associated with leukoencephalopathy include bortzemoib, gemcitabine, sunitinib, cisplatin, and oxiplatin [124–131]. Treatment for these

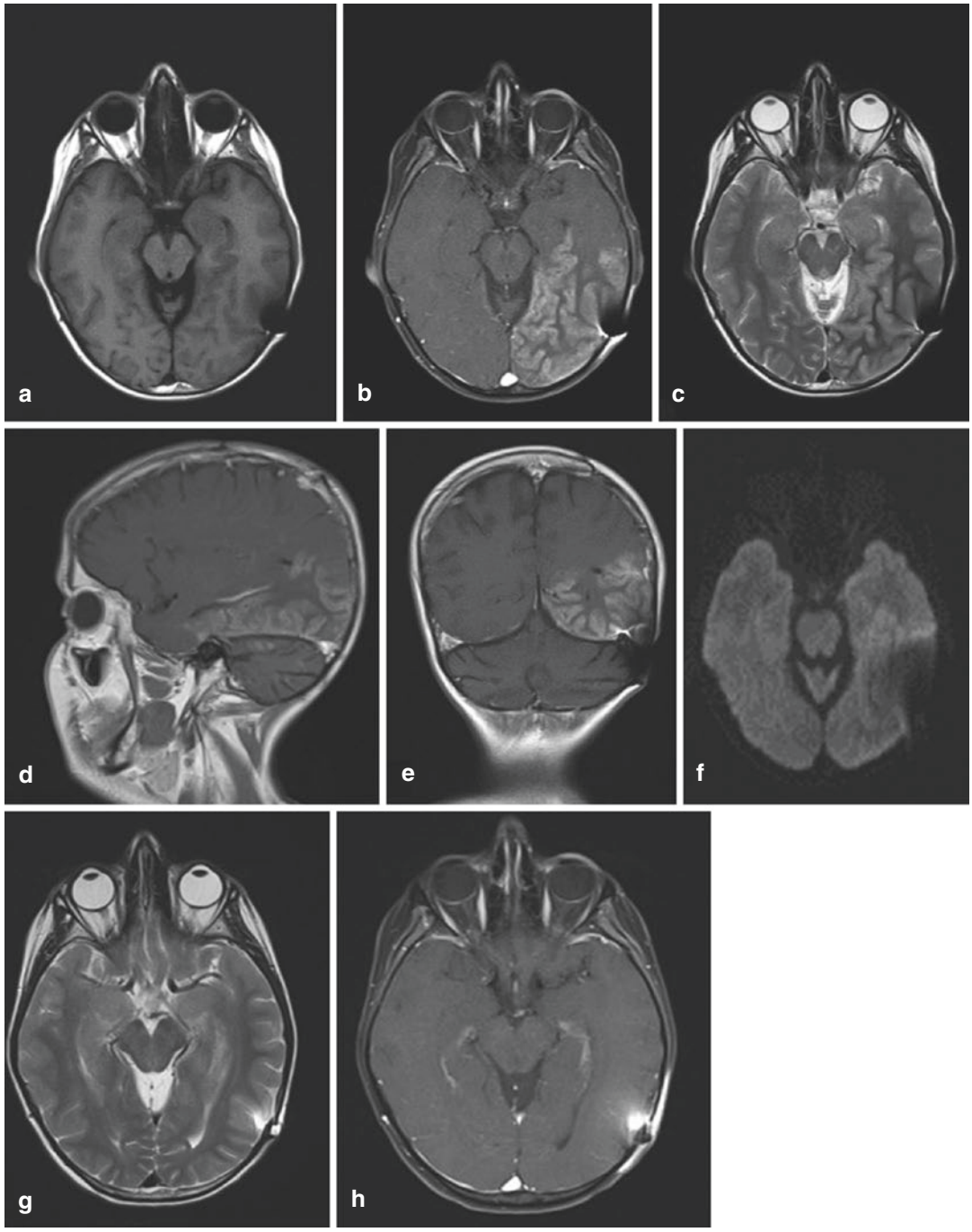

Fig. 15.26 **SMART syndrome**. 30-year-old male with VP shunt presents with progressive left-sided headache, language difficulties, right arm numbness, and weight loss. History of medulloblastoma status-post excision, chemotherapy and radiation 24 years before. **Right**: Imaging on presentation with pre contrast T1 (**a**) and gyriform cortical enhancement in the left temporo-occipital region (**b**, **d**, **e**) and no definite restricted DWI (**f**). **Left**: Imaging resolution on follow-up (**g h**)

neurotoxicities as detailed in case reports generally involve removal of the offending agent, supportive care including anti-seizure medications, and control of comorbidities, especially hypertension.

15.3.2 Heroin-Induced Spongiform Leukoencephalopathy

There is no proven treatment for heroin-induced spongiform leukoencephalopathy. However, some manuscripts have reported varying levels of improvement with antioxidants including coenzyme Q10 on its own or in combination with vitamin E and vitamin C [132, 133].

15.3.3 Cocaine, Phencyclidine Hydrochloride, Amphetamines, and Related Catecholaminergics

Management for these toxicities begins first and foremost with establishment of airway, breathing, and circulation. Should intubation be required, succinylcholine should be avoided, as it is a strong acetylcholine receptor agonist that produces sustained depolarization and has a well-established risk of rhabdomyolysis as compared to non-depolarizing neuromuscular blocking drugs [134].

Following resuscitation, treatment relies largely on attenuating CNS release of catecholamines and treating the sequelae of sympathetic activation. Intermediate to long-acting benzodiazepines including lorazepam and diazepam are first-line agents for acute cocaine, phencyclidine hydrochloride, and amphetamine toxicity, lowering blood pressure, attenuating hyperthermia, and decreasing agitation [135–137]. For hypertension resistant to benzodiazepines, short-acting vasodilators including nitroglycerin and nitroprusside are employed, while residual tachycardia may be treated with calcium channel blockers. If myocardial infarction is suspected or diagnosed, appropriate therapeutic steps should be taken.

15.3.4 Hypoxic–Ischemic Encephalopathy

Management of hypoxic-ischemic encephalopathy (HIE) varies by age. In adults, supportive and preventive care is the standard [138–140]. Seizures may be treated with appropriate anti-seizure medications, and myoclonic seizures specifically may be treated with valproate or clonazepam [141]. Patients may also present with post-hypoxic myoclonus, which case reports have been responsive to phenytoin, phenobarbitone, or benzodiazepines [142]. Limited evidence exists for the treatment of subclinical seizures [143].

In neonates, the only protective strategy that has shown consistently benefit has been therapeutic hypothermia, started within the first 6 h after delivery [144]. Mechanistically, it is thought to reduce free radicals and glutamate levels, decrease oxygen demand, and decrease apoptosis [145]. This should be supplemented with supportive care, including volume support, management of seizures with phenobarbital, lorazepam, fosphenytoin, or levetiracetam, and respiratory therapy for infants with persistent pulmonary hypertension to maintain oxygenation.

15.3.5 Hypoglycemia and Hyperglycemia

Treatment is specific to etiology of the glucose imbalance (Table 15.1).

First, we consider hypoglycemia in patients with type 1 or type 2 diabetes. By far, the most commonly implicated etiology is medication. Preventive strategies around this include setting glycemic targets, establishing consistent medication regimens, recognizing signs and symptoms of hypoglycemia early, and ingesting bedtime snacks to prevent nocturnal hypoglycemia. If hypoglycemia does arise, treatment may vary from ingesting fast-acting carbohydrates and retesting blood glucose if the patient is asymptomatic or mildly symptomatic to administering glucagon or IV dextrose if the patient is severely symptomatic [146, 147].

Table 15.1 Etiologies of hypo- and hyperglycemia by diabetes status

	Without diabetes	With diabetes
Hypoglycemia	Medications Alcohol Cortisol deficiency Insulinoma/excess insulin Critical illness/sepsis	Medications
Hyperglycemia	Stress-induced Acute myocardial infarction	Type 1 diabetes Type 2 diabetes Hyperosmotic hyperglycemia state (HHS)/diabetic ketoacidosis (DKA)

Next, we address patients with diabetes who present with hyperglycemia. In patients with type I diabetes, physicians should adjust their insulin regimen and address their dietary habits. In patients with type II diabetes, management begins with lifestyle changes including diet, exercise, and weight loss. Should this be unsuccessful, the first-line treatment is metformin, with a glycemic treatment goal of HgbA1c goal of <7.0 in younger adults without complications or 8–8.5 depending on advanced age, comorbidities, and life expectancy [148, 149]. If within 3 months, the glycemic treatment goal is not achieved with metformin along with lifestyle intervention, a second agent may be prescribed. Following that, triple agent therapy and bariatric surgery are third-tier options, though recurrences of diabetes in the latter are not uncommon and microvascular and macrovascular complications are comparable to those of medical therapy [150, 151]. Medications should be prescribed as tolerated with additional comorbidities (such as obesity) in mind. In patients in diabetic ketoacidosis (DKA) or hyperosmotic hyperglycemic state (HHS), the overriding principles are to correct fluid and electrolyte abnormalities, administer insulin, and monitor laboratory parameters closely until the anion gap closes [152]. The use of sodium bicarbonate has been widely debated, as side effects include peripheral hypoxemia, paradoxical CNS acidosis, and cerebral edema in children and young adults [153–155]. However, a general consensus has been formed around its use strictly in adults when arterial pH is less than 7.0 or when potentially life-threatening hyperkalemia (>6.4 mEq/l) is present [156–158].

If hypoglycemia occurs in patients without diabetes, treatment should be targeted at the underlying etiology of the low blood sugar. Again, medications are a widely implicated cause. A number of common medications have a known side effect of hypoglycemia, such as pentamidine, quinine, and indomethacin [159]. Other medications less commonly but still associated with hypoglycemia include lithium and IGF-1 [160]. Physicians should adjust medication regimens as appropriate, titrating therapeutic effects to each patient. Chronic alcoholism is also associated with hypoglycemia, and should be treated with dietary counseling and support around alcohol cessation [161]. Cortisol deficiency secondary to Addison's disease may be treated with cortisone therapy, and sepsis should be managed with appropriate resuscitation and treatment of the offending organism. While a relatively uncommon cause of hypoglycemia, insulinomas may be treated with resection of primary tumor, ethanol ablation, or medical management with diazoxide, octreotide/lanreotide if refractory to diazoxide, or verapamil [162–164].

Finally, hyperglycemia in patients without diabetes and with appropriately drawn labs could be attributable to stress-induced hyperglycemia (SIH), an enhanced metabolic state induced after trauma [165]. Attempts at tight glycemic control in both ICU and non-ICU patients do not improve outcomes, and the ideal glucose parameters under this condition are unclear as spontaneous improvement in fasting blood glucoses is inconsistently found in some patients with SIH [166]. However, a general target range between 100 and 180 mg/dl has been suggested by experts [167].

15.3.6 Carbon Monoxide Intoxication

If exposed to excessive quantities of carbon monoxide (CO), patients should be immediately removed from the source of the CO and administered 100%, high-flow oxygen via a nonrebreather mask. In most cases, such treatment will be successful in resolving symptoms. However, patients with persistent symptoms or EKG or lab findings suggestive of severe poisoning should be hospitalized. Additionally, if patients become comatose or unable to protect their airway, they should be intubated immediately [168].

The benefit of hyperbaric oxygen is unclear. Randomized control trials have shown mixed effects of hyperbaric treatment, and one meta-analysis conducted in 2011 demonstrated no statistically significant difference between treatment and control [169, 170]. However, studies have been heterogeneous, with variable outcome measures. In general, hyperbaric treatment is recommended if any of the following are present: loss of consciousness, new neurologic impairments, end-organ ischemia, or pregnancy [171].

15.3.7 Delayed Postanoxic Encephalopathy

Following emergence of delayed postanoxic encephalopathy, treatment is supportive with active rehabilitation [172]. If Parkinsonian symptoms arise, case reports have described successful use of carbidopa and haloperidol [50, 173, 174]. Outcomes are generally positive.

15.3.8 Osmotic Demyelination

Prevention is crucial toward avoiding these demyelination syndromes, with slow (less than 6–8 mEq/l correction every 24-h period) correction in patients with hyponatremia lasting more than 2 days or with hyponatremia of unknown duration. Should an osmotic demyelinating syndrome arise, treatment is largely supportive, with careful monitoring of serum sodium concentration every 2–3 h initially.

While less commonly employed, case reports have demonstrated benefit from lowering sodium levels [175–177]. As such, desmopressin has been administered for its antidiuretic effects along with fluid replacement with dextrose if excessive urinary-free water loss is present [178, 179]. Additionally, one case report detailed symptomatic improvement in two of three patients following plasmapheresis. However, imaging remained unchanged, and spontaneous self-resolution of neurologic impairment has been previously observed [180].

15.3.9 Wernicke Encephalopathy

Immediate parenteral administration of thiamine is required after diagnosis, with a transition to oral vitamin B1 as tolerated [181]. Even after treatment, patients with thiamine insensitivity may necessitate higher than normal levels of thiamine [182]. If patients are hypoglycemic as well, case reports and series have suggested that glucose administration prior to thiamine might be a risk factor for development of Wernicke encephalopathy [183]. Regardless, correction of hypoglycemia should be either concurrent with or immediately preceded by administration of thiamine. Following appropriate management, patients should be counseled on dietary requirements of B vitamins and alcohol cessation if abuse or overuse is present.

15.3.10 Marchiafava–Bignami Disease

Similar to Wernicke encephalopathy, Marchiafava-Bignami disease is associated with chronic alcoholism, so treatment aimed at correcting underlying nutritional and vitamin imbalances is often

employed. Parenteral thiamine has been associated with better outcomes, especially during the acute phase of the illness compared to chronic disease. Additionally, a case report has documented benefit with steroids. However, the disease has poor prognosis overall, therapeutic failure is often seen even after supplementation of B1, and a case series by Hillbom et al. showed no statistically significant improvement in 150 patients with steroid treatment [41, 184, 185]. A subset of surviving patients develops subsequent dementia, though partial or complete spontaneous recovery has been reported in some of these cases [184].

15.3.11 Steroid-Responsive Encephalopathy Associated with Autoimmune Thyroiditis (Hashimoto's Encephalopathy)

A vast majority of patients respond well to high-dose steroids with duration and tapering titrated to improvement in symptoms [186]. Other therapeutics including IV immunoglobulins, plasmapheresis, and immunomodulators such as methotrexate, azathioprine, and mycophenolate have been used with variable success in patients who have been steroid-intolerant [187–190].

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15.4 Brain Death Management

Deema Fatal

15.4.1 History of Brain Death Concept

Brain death criteria is a new concept that was developed in the twentieth century as a result of improvements in intensive care of comatose patients, including unresponsive patients. The concept of brain death was first noted in the medical literature in 1959 by Mollaret and Goulon, which they called irreversible coma (coma dépassé) [191]. During the 1950s, advances in positive pressure ventilators led to patients, who would have died otherwise, to remain alive but without being responsive. As a result of such situations, neurologists had ongoing debates about these patients throughout the 1960s, and such debates were ongoing across the globe too, in Great Britain, Switzerland, South Africa, and Australia [192]. In 1967, anesthesiologist Henry Beecher led a committee to review the "ethical problems created by the hopelessly unconscious patient" [192]. This culminated in 1968 in the Harvard report on brain death [193]. This report was the first to put forth specific criteria for brain death [192]. The purpose of the report was to "define irreversible coma as a new criterion for death" and to discuss the ethical issue of procuring organs from such patients for transplantation; and both these issues were mentioned in the final report: "(1) the burden is great on patients who suffer permanent loss of intellect, on their families, on the hospitals, and on those in need of hospital beds already occupied by these comatose patients; (2) obsolete criteria for the definition of death can lead to controversy in obtaining organs for transplantation" [193]. The Harvard report's brain death criteria were the following: a person can be declared dead if there is (1) unreceptivity and unresponsivity even to the most intensely painful stimuli; (2) No movements (observed for 1 h) or breathing (upon turning off the ventilator

for 3 min); (3) No reflexes (pupil, calorics, dolls eyes, corneal, and pharyngeal reflexes, and no swallow, yawning, or vocalization); and no stretch reflexes; (4) Flat EEG recorded for at least 10 min [193]; all this should be repeated 24 h later. Moreover, hypothermia <90 °F and depressants such as barbiturates should be excluded [193].The Harvard criteria were not legally binding [192]. Yet over the ensuing decade, the concept of brain death spread and during the 1970s some states started to develop brain death criteria, making it possible to be alive in one state and dead in another [192].

To overcome the confusion related to brain death across the states, there was a need for regulation at the federal level. In 1981, The President's Commission report for the "Study of Ethical Problems in Medicine and Biomedical and Behavioral Research" led to a proposal for a legal definition for brain death, which, in turn, resulted in the Uniform Determination of Death Act (UDDA) [194]. UDDA states that "An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made with accepted medical standards" [195]. Over time, all 50 states adopted one version or another of UDDA.

Though brain death was now defined in all states, confusion related to the exact criteria of brain death remained. The UDDA did not define "accepted medical standards." So in 1995, the American Academy of Neurology (AAN) published practice parameter to delineate the medical standards for the determination of brain death [196] and updated them in 2010 [197].

15.4.2 Diagnostic Criteria for Brain Death

To define brain death, three specified parameters need to be followed which are (1) Coma: irreversible cessation of all functions of the entire brain, including the brain stem due to a known condition that can cause brain death; (2) absence of brainstem reflexes; and (3) apnea. In other words, brain death is declared when "brainstem reflexes, motor responses, and respiratory drive are absent in a normothermic, non-drugged comatose patient with a known irreversible massive brain lesion and no contributing metabolic derangements" [198]. Typically, cardiac death occurs within few days of brain death [199], but not uniformly—the case of Jahi McMath [192]. It is important to note that once the AAN criteria for brain death determination were followed completely, no one has been reported to recover [197].

15.4.3 Neuropathology

In the past, the neuropathology of brain-dead patients showed total brain necrosis, so-called respirator brain [200]. But, with the advent of transplantation protocols, brain fixation is occurring in a timely fashion. In 2008, Wijdicks and Pfeifer reviewed neuropathology of 41 brains from brain dead patients where the autopsy was done within 36 h of brain death [200]. The findings were the following: (1) there are no pathognomonic feature; and (2) severe pathology was not uniform; in fact, mild changes were seen in as much as one-third of cerebral hemispheres and half of the brainstems [200].

15.4.4 Brain Death Causes

Known causes of brain death are intracranial hemorrhage, subarachnoid hemorrhage, large strokes with edema and herniation, hypoxic-ischemic injury, severe trauma, and fulminant hepatic necrosis with cerebral edema and increased intracranial pressure [201]. In fact, 90% of brain death causes are brain trauma, intracranial hemorrhage, subarachnoid hemorrhage, stroke, and anoxia [202].

15.4.5 Brain Death Mimickers

Severe clinical conditions can present in coma and could potentially be confused with brain

Table 15.2 Brain death examination

Unresponsive to verbal/pain stimuli
Temperature > 36 °C
Systolic blood pressure BP ≥ 100
Pupils fixed mid position
No corneal reflex
No gag, cough reflexes
No oculocephalic or oculovestibular reflexes
No grimace to facial pain
No response to pain to all limbs

death: fulminant Guillain-Barré syndrome, organophosphate intoxication, high cervical spinal cord injury, lidocaine toxicity, baclofen overdose, and delayed vecuronium clearance [197]. Yet review of these cases showed that none had a complete brain death examination using the AAN practice parameters [197].

15.4.6 Determination of Brain Death

To determine brain death, using AAN 2010 guidelines [197], the following criteria are needed:

1. Known irreversible cause
2. No confounding factors (such as no paralytic agents, sedatives, hypnotics, drugs, alcohol, or severe electrolytes, acid base, or endocrine disturbances)
3. Complete brain death examination—see Table 15.2.
4. Apnea test

The lack of need for a second exam was shown in a study by Lustbader et al. [203]. They studied 1229 brain dead adult bodies and 82 pediatrics. None regained brainstem function upon repeat examination. The time between the two exams was 19 h. Consent for organ donation decreased from 57 to 45% as the brain death declaration interval increased. Twelve percent sustained cardiac arrest between the first and second examination.

It is important to note that the apnea test cannot be completed in about 10% [204]. This is where the role of radiological tests may become relevant.

15.4.7 Future Directions

The biggest consequence of brain death criteria has been the ability to procure organs and save lives. But the definition of brain death has remained challenging. First, many versions of brain death criteria exist across the USA and the globe [198, 205]. In one study, 80 countries were surveyed and major discrepancies were found, such as PCO2 target was recommended in only 59% of the protocols [198]. Second, the concept of brain death has been difficult to conceptualize. Is the brain essential for the function of the whole organism, so that a dead brain means a dead organism [206]? This argument did not hold water over time since brain dead patients, with support of artificial feeding and ventilation, can remain stable for years, and can even give birth, negating the claim that the brain is essential for the functioning of the whole body [207]. In 2008, president's council on bioethics addressed this issue in its white paper "controversies in the determination of death" [208]. Although brain dead patients can remain stable and maintain "integrated functioning," they are still dead because "they have ceased to perform the fundamental vital work of a living organism" [192]. However, this concept too is on shaky grounds: the lack of ability to perform a vital function as criteria for death is confusing since a patient who has pneumonia and needs a ventilator cannot perform a vital function yet s/he is not dead. As 3-D printing of organs and tissues and xenotransplantation science continues to evolve, it is possible that the need for organ donation will become obsolete, making brain death definition less important in the future [192]. Until then, brain death concept remains, 50 years later, "well settled, yet still unresolved" [192].

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