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Introduction

Encephalopathy is the term used to describe a general alteration in brain function, manifesting as an attentional disorder anywhere within the continuum between a hyperalert agitated state and coma. In clinical practice, the diagnosis of encephalopathy is usually reserved for the diffuse brain dysfunction felt to be due to a systemic, metabolic, or toxic derangement, rather than, for example, a multifocal structural process; therefore the adjectives “metabolic” or “toxic-metabolic” are usually implied when the diagnosis of encephalopathy is made. The syndrome of toxic-metabolic encephalopathy is essentially synonymous with *delirium*, the term favored by most nonneurologists. Autoimmune encephalopathies are another important mechanism of diffuse brain dysfunction; these syndromes—technically more consistent with “encephalitides” than “encephalopathies”—are characterized by suggestive clinical and laboratory features and response to immune-based therapies (and sometimes removal of an underlying neoplasm), distinguishing them from the toxic-metabolic encephalopathies discussed in this chapter.

Neurologists are frequently asked to evaluate patients with alteration in consciousness from a toxic-metabolic encephalopathy. The consulting physician likely requests the neurologic consultation because of concern for a structural, ischemic, epileptic, or other focal primary neurologic causes of the patient’s encephalopathic symptoms. The neurologic diagnosis of a toxic-metabolic encephalopathy is typically made by finding characteristic diffuse clinical symptoms and (mostly) nonlocalizing findings within the appropriate clinical context, usually with exclusion of other processes through imaging and other studies. The diagnosis of toxic-metabolic encephalopathy may lead to the generic and appropriate recommendation to correct any metabolic abnormalities, treat any underlying acute systemic illness, and discontinue or limit the use of sedatives or other medications with central nervous system side effects. In many cases, though, a more specific diagnosis can be made, and prompt recognition of the causative systemic process or medication can lead to a more rapid neurologic recovery, or in some cases, prevention of irreversible neurologic injury [1].

The purpose of this chapter is to discuss an approach to the emergency evaluation of patients with encephalopathy, with an emphasis on those causes of toxic-metabolic encephalopathy that will lead to irreversible neurological dysfunction if not recognized and treated urgently, as well as the encephalopathies whose recognition—by clinical or neuroimaging findings—might lead to

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more prompt diagnosis and treatment of the causative medical illness.

Epidemiology of Toxic-Metabolic Encephalopathy

The evaluation of encephalopathy is a common aspect of day-to-day neurologic practice, and encephalopathy can occur in any patient at any age with a severe systemic illness or with exposure to a metabolic or toxic derangement causing cerebral dysfunction. The epidemiology of toxic-metabolic encephalopathy, however, is best characterized for hospitalized older adults. Approximately one-third of general medical patients 70 years of age or over have delirium, which may be present on admission or after; in addition, delirium is common after surgery (up to 50% after high-risk procedures) and is most common in patients in the intensive care unit (with a prevalence of over 75%) and at the end of life [2]. Delirium is also associated with an increased risk of mortality; a 2010 meta-analysis found a nearly twofold increased risk of death after an average follow-up of 22.7 months in elderly patients with delirium compared to those without delirium [3]. These statistics underscore both the ubiquity of this clinical syndrome and the fact that encephalopathies are usually reflective of severe underlying acute systemic disease and dysfunction.

Pathophysiology of Toxic-Metabolic Encephalopathy

A detailed discussion of the underlying pathophysiology of each of the many causes of toxic-metabolic encephalopathy is outside the scope of this chapter. However, among the many mechanisms of global neuronal and glial dysfunction that can occur due to metabolic or toxic derangements, general pathophysiologic mechanisms that underlie many of these clinical syndromes include creation of an energy deficit through a decrease in the level of basic metabolic substrates necessary for neuronal survival; oxidative stress; and functional alterations of neurotransmitter

systems, including alterations in neurotransmitter synthesis and release [4].

From an emergency management perspective, brain survival is the primary goal, so it is particularly critical to recognize and immediately treat those pathophysiologic causes of metabolic encephalopathy that may directly result in cell death due to loss of neuronal energy substrates (e.g., glucose, oxygen, and thiamine) in order to prevent irreversible neuronal death and to increase the likelihood of clinical neurologic recovery. It is also critical to immediately recognize those systemic processes that can secondarily cause irreversible neuronal injury, for example, by causing increased intracranial pressure (ICP) and potential cerebral herniation (e.g., acute hepatic encephalopathy from fulminant hepatic dysfunction). On the other hand, all causes of toxic-metabolic encephalopathy share the underlying pathophysiology of usually severe and often life-threatening systemic illness and dysfunction, underscoring the importance of accurate diagnosis and medical or surgical treatment no matter what the underlying systemic process is.

Although the basic underlying cellular pathophysiology of metabolic encephalopathies may differ, they share a common mechanism of generalized, rather than focal, alteration in hemispheric and brainstem dysfunction, leading clinically to a diffuse alteration in attention and arousal. Some encephalopathic syndromes, however, preferentially affect certain vulnerable brain regions specific to the underlying cause of the encephalopathy, such as the medial thalamic and periaqueductal gray matter in thiamine deficiency.

Clinical Features of Toxic-Metabolic Encephalopathy

Patients with toxic-metabolic encephalopathy typically present with a global alteration in level of alertness, varying between and within patients, from obtundation and coma to an agitated delirium. The time course of development of the encephalopathy can vary from rapid (e.g., from acute hypoglycemia, hypoxia, or drug overdose)

to the more common subacute presentation from insidiously developing systemic disease processes.

On clinical examination, patients with encephalopathy are often lethargic, confused, or agitated, typically without obvious focal localizing neurologic features. Many patients with toxic-metabolic encephalopathies exhibit asterixis, elicited by asking the patient to hold his or her arms outstretched. Asterixis is manifested by a very brief loss of postural tone of the outstretched arms. It is not necessary for the wrists to be dorsiflexed to evaluate for asterixis; however, if the patient is able to perform this, the classic “flap” of brief downward wrist flexion may be observed. The finding of bilateral asterixis is rather specific, but not sensitive, for the presence of a toxic-metabolic encephalopathy from a number of potential processes but is not pathognomonic for any particular cause of the encephalopathy. In clinical practice, though, asterixis is commonly associated with uremic or hepatic encephalopathies.

Although the hallmark of toxic-metabolic encephalopathies is disordered attention, seizures can occur in some syndromes as well, particularly when severe; these include disorders such as hypoglycemia and hyperglycemia, some electrolyte disorders, acute hepatic failure, and various medication-related encephalopathies (see the Section “[Encephalopathic Syndromes](#)”).

Diagnosis of Toxic-Metabolic Encephalopathy

As when taking any neurologic history, the physician should delineate the clinical neurologic symptoms and their time course (especially from witnesses if the patient is unable to provide a history), carefully detailing the current systemic context, other medical comorbidities, and all current and recent medications. Examination should focus not only on the mental status (especially level of consciousness) and generalized neurologic findings expected in a diffuse encephalopathy, including assessment for asterixis, but should also focus on assessing vital signs; signs of men-

Table 15.1 Examination of the patient with encephalopathy

Level of consciousness
Vital signs
Passive flexion of the neck for meningismus
Funduscopy examination for papilledema
Language (looking for aphasia)
Neurological examination for cranial nerve or focal motor deficits and asterixis

ingeal irritation; observation for aphasia (especially the fluent kind as a mimic of a confusional state); funduscopy examination for signs of increased intracranial pressure; and exclusion of obvious motor or other asymmetries for which an alternative diagnosis may be more likely (Table 15.1).

Despite the diffuse neurologic presentation of patients with a probable toxic-metabolic encephalopathy, diagnostic evaluation often necessitates brain imaging studies (CT or MRI) to rule out causative focal structural or ischemic lesions, especially if there is any uncertainty as to the diagnosis. Although these imaging studies are typically performed to exclude focal structural or ischemic processes, and should therefore not demonstrate a focal structural lesion in the patient ultimately diagnosed with a diffuse encephalopathy, some toxic-metabolic processes are themselves associated with abnormal imaging features that may be helpful in diagnosis [5] and are discussed further in the Section “[Encephalopathic Syndromes](#)”.

EEG can be helpful in the evaluation of the patient with encephalopathy, particularly when subclinical status epilepticus is a diagnostic consideration. Diffuse slowing on the EEG is a nonspecific and nearly ubiquitous finding in these patients, simply paralleling the clinical syndrome of a diffuse cerebral process. The EEG finding of triphasic waves is rather specific, but not sensitive, for a toxic-metabolic encephalopathic process but is not diagnostic as to the actual cause; however, like asterixis, in clinical practice triphasic waves are often seen in patients with hepatic and uremic encephalopathies.

Laboratory testing is the mainstay of investigation of the etiology of toxic-metabolic

Table 15.2 Diagnostic studies for the patient with an encephalopathy

Blood pressure, serum glucose, and O ₂ saturation
Comprehensive metabolic panel and ammonia level
Complete blood cell count with differential
Urinalysis and culture, urine tox screen
Blood cultures
Brain MRI or CT
EEG
Spinal fluid analysis if indicated

encephalopathy. Serum glucose testing (including rapid finger stick determination as well as laboratory analysis of a drawn blood sample) and pulse oximetry should be immediately assessed in all patients because of the potentially irreversible nature of hypoglycemic and hypoxic brain dysfunction unless rapidly diagnosed and treated. A complete metabolic profile (including serum electrolytes and liver and kidney function tests) will quickly assess for the most common metabolic and systemic abnormalities, and a complete blood cell count will quickly exclude profound anemia and an elevated white blood cell count while also looking for clues to an underlying systemic infectious process.

Lumbar puncture (LP) will show only nonspecific, if any, cerebrospinal fluid (CSF) abnormalities in a patient with a toxic-metabolic encephalopathy; however, this should be performed when there is any clinical concern for meningoencephalitis (including autoimmune encephalitis) or subarachnoid hemorrhage. Lumbar puncture in the encephalopathic patient typically should be performed only after screening emergent neuroimaging (most commonly a noncontrast head CT) has excluded a focal cerebral mass lesion (e.g., abscess or hematoma) which might be a contraindication to this procedure. Table 15.2 lists the diagnostic studies for the patient with an encephalopathy.

Encephalopathic Syndromes

Patients with diffuse toxic-metabolic encephalopathies are medically, and secondarily neurologically, ill. Therefore, despite the ubiquity of

these clinical syndromes in typical inpatient neurological consultative practice, evaluation of patients with diffuse encephalopathies represents a unique and critically important opportunity for the neurologist to positively impact the medical management, and both the neurological and medical recovery, of these severely systemically ill patients.

This section outlines four common and distinct (but overlapping) presentations the clinician is likely to encounter in clinical practice: encephalopathy from a basic metabolic disorder or deficiency, encephalopathy due to a severe systemic illness or organ failure, encephalopathy due to medication-related toxicity, and encephalopathies diagnosable primarily by findings on brain imaging.

Encephalopathy from Basic Metabolic Disorder or Deficiency

Oxygen, Glucose, and Electrolytes

As stated earlier, hypoxemia and hypoglycemia are critical to consider and be quickly excluded in any encephalopathic patient, as deficiencies of these basic and critical neuronal energy substrates will lead to irreversible neuronal death unless recognized and reversed quickly; most other metabolic disorders are less likely to directly lead (or lead quickly) to neuronal cell death and irreversible injury. Likewise, profound hypotension or anemia can lead to loss of energy supply to neurons and should be excluded quickly via immediate assessment of vital signs, oxygen saturation, and hemoglobin concentration; careful therapeutic attention should be placed on these basic emergency resuscitation parameters in all encephalopathic patients as in any critically ill patient.

In addition to hypoxemia and hypoglycemia, encephalopathy frequently occurs in the setting of hyperglycemia and of certain electrolyte abnormalities, especially hyponatremia, hypernatremia, and hypercalcemia. Though hyperkalemia and hypokalemia are well-known causes of neuromuscular dysfunction (and of cardiac dysfunction which can secondarily cause

hypoxic-ischemic encephalopathy), these common abnormalities of potassium concentration are not typically associated with encephalopathy.

Thiamine Deficiency (Wernicke's Encephalopathy)

Thiamine (vitamin B1), in the form of its active phosphorylated derivatives (especially thiamine diphosphate, also called thiamine pyrophosphate), is an important coenzyme in a number of intracellular enzymatic activities, including energy production and various biosynthetic pathways. Deficiency of thiamine causes Wernicke's encephalopathy, characterized classically by the clinical triad of ophthalmoplegia, mental status changes, and ataxia. This is a very important cause of encephalopathy due to the potential irreversibility of clinical findings and especially because of the development of an irreversible amnestic state if thiamine deficiency is not recognized and treated emergently [6, 7]. Although commonly thought of as a disease of patients with alcohol dependence, Wernicke's encephalopathy can occur due to any process that leads to inadequate absorption or intake of thiamine, including hyperemesis states such as hyperemesis gravidarum, malnutrition from any cause, bariatric surgery, chronic diarrheal illnesses, and in the course of many systemic illnesses [7, 8].

Despite the commonly memorized clinical triad, the clinical symptoms and signs in patients with Wernicke's encephalopathy vary, and the full triad is usually not present in an individual patient. The most common symptom is mental status change, manifesting as agitation and confusion or apathy, and can progress to coma. Eye findings, if present, most commonly include nystagmus and sometimes sixth nerve palsies; complete "ophthalmoplegia," as listed in the classic triad, is actually rare. Ataxia of gait is often present. Other signs and symptoms that may be seen in patients with Wernicke's encephalopathy include hypothermia, hypotension, and tachycardia [7].

Brain regions commonly involved in Wernicke's encephalopathy include the mammillary bodies, periaqueductal gray matter, and

medial thalami; changes in these regions may be seen on diffusion-weighted and T2-weighted MRI in some patients with Wernicke's encephalopathy. These particularly vulnerable brain regions explain the characteristically severe, and potentially irreversible, amnestic state (called *Korsakoff's syndrome*) that occurs in patients with Wernicke's disease if prompt treatment is not initiated.

Because of the treatable aspect of this condition, and its neurological irreversibility if not treated in a timely fashion, neurologists need to keep this diagnosis in mind in all patients presenting with encephalopathy, whether or not other features of the syndrome (e.g., nystagmus or gait ataxia) are present. The diagnosis is typically entirely clinical; thiamine levels are not useful in practice, especially due to delay in obtaining these results. Although MRI findings can be seen in some patients with Wernicke's encephalopathy, these findings are insensitive for the diagnosis; importantly, one of the priorities is to try to make the clinical diagnosis and begin treatment before the development of any of the characteristic imaging findings.

Treatment with parenteral thiamine should be initiated emergently in any patient in whom the diagnosis is a reasonable consideration and must be given prior to any glucose administration due to the risk of glucose precipitating or worsening Wernicke's encephalopathy. Although the optimal evidence-based dose of thiamine is uncertain, expert recommendations suggest that initial parenteral thiamine dosing should be >500 mg daily, given as a once- or divided-daily regimen, for 3–5 days [7, 9].

Encephalopathy Due to Severe Systemic Illness or Organ Failure

Severe Systemic Illness and Septic Encephalopathy

As discussed in the preceding sections (and inherent in the diagnosis of the clinical syndrome of a toxic-metabolic encephalopathy), encephalopathies commonly occur in the setting of a severe underlying systemic illness.

Encephalopathy is especially common in patients in the medical ICU [10, 11] and in patients whose illness may be severe enough to warrant transfer to a medical ICU setting. Any medical illness of sufficient severity can lead to the clinical syndrome of a toxic-metabolic encephalopathy; in addition, the common finding of encephalopathy in the specific clinical setting of systemic sepsis, with or without multiorgan failure, has led to the designation of the term *septic encephalopathy* [12]. The pathophysiology of septic encephalopathy is unclear, although theoretical mechanisms include the effects of inflammatory mediators, blood-brain barrier dysfunction, and other possible metabolic effects of the severe systemic dysfunction [12]. As in any severe systemic infectious illness, encephalopathy has been reported to be common in patients hospitalized with SARS-CoV-2, with one recent multicenter report finding that of 817 older adults with SARS-CoV-2, delirium was seen on presentation in 28% of patients, and was associated with an increased risk of poor hospital outcomes and death [13]. In another study, encephalopathy was found to be present during the disease course in 31.8% of a consecutive series of 509 patients admitted with confirmed SARS-CoV-2 to a hospital network; these researchers found that encephalopathy was associated with worse functional outcome and higher mortality within 30 days of discharge, independent of the severity of respiratory disease [14].

Although sepsis or severe acute medical (including infectious) illnesses of any cause are common etiologies of encephalopathy, encephalopathies also occur due to single-organ dysfunction or failure. In each of these clinical scenarios, the neurologist is important in diagnosing the causative medical illness, which may have a direct impact on systemic treatment and the course of neurologic improvement. The specific single-organ causes of encephalopathy discussed below include hepatic encephalopathy, uremic encephalopathy, pancreatic encephalopathy, and the fat embolus syndrome.

Hepatic Encephalopathy

Hepatic encephalopathy can occur in patients with either chronic liver disease (cirrhosis) or

acute liver failure [15]. Encephalopathy due to chronic liver disease typically progresses slowly, with the clinical features defined in stages, or grades; minimal hepatic encephalopathy is characterized by subtle findings detectable mainly by formal neuropsychological testing: grade I is characterized by psychomotor slowing and lack of attention; grade II is characterized by disorientation, lethargy, and unusual behavior; grade III is characterized by somnolence and stupor; and patients in grade IV hepatic encephalopathy are in coma [16].

Asterixis is most commonly associated with grade II hepatic encephalopathy but can also be seen in other stages. Chronic liver diseases in some patients present as a slowly progressive parkinsonian syndrome, sometimes referred to as acquired (non-Wilsonian) hepatolenticular (or hepatocerebral) degeneration consisting of bradykinesia, rigidity, tremor, dysarthria, and ataxia [17]. Seizures are uncommon in patients with hepatic encephalopathy due to chronic liver disease.

The diagnosis of hepatic encephalopathy due to cirrhosis is made by observing the characteristic neurological clinical features in the appropriate clinical context. Ammonia levels remain helpful in the clinical diagnosis of hepatic encephalopathy, although these levels do not correlate well with the various stages of encephalopathy and a normal serum ammonia level does not exclude the diagnosis of hepatic encephalopathy. As mentioned in the earlier Section “[Diagnosis of Toxic-Metabolic Encephalopathy](#),” triphasic waves may be seen on EEG in some patients with hepatic encephalopathy, but this finding is neither sensitive nor specific for this condition. The MRI finding of high signal in the bilateral globus pallidus on noncontrast T1-weighted images has been attributed to manganese deposition in the brain due to reduced biliary manganese excretion; this MRI finding, however, is common in patients with chronic liver disease, whether or not a clinical encephalopathy is present [17].

Treatment of hepatic encephalopathy is aimed at reducing ammonia absorption through the use of nonabsorbable disaccharides, such as lactulose,

and reducing ammonia production through the use of antibiotics such as rifaximin [18].

In contrast to patients with chronic cirrhosis and portosystemic shunting, acute liver failure commonly presents as rapidly progressive neurologic deterioration leading to life-threatening cerebral edema, with coma and seizures [19]. The neurologic assessment and treatment of patients with acute hepatic encephalopathy consist of ICP monitoring with aggressive reduction of increased ICP and management of any associated seizures.

Uremic Encephalopathy

Encephalopathy can occur due to either acute or chronic renal failure and typically develops more rapidly in patients with acute kidney dysfunction [20]. Symptoms of uremic encephalopathy include asterixis, myoclonus (uremic twitching), and coarse tremor; seizures may also be seen. The clinical symptoms and signs, including the EEG finding of triphasic waves in severe uremic encephalopathy, mimic those of many other metabolic encephalopathies; however, the tremulousness and twitching seen in many patients with uremic encephalopathy may be somewhat more suggestive of this cause of encephalopathy compared to other systemic processes.

The diagnosis of uremic encephalopathy is clinical, supported by appropriate laboratory studies showing severe kidney dysfunction, along with the reasonable exclusion of other potentially causative systemic, or other, processes. Other systemic causes of encephalopathy that especially need to be considered in the uremic patient include drug toxicities (especially those that are renally metabolized or excreted), electrolyte disturbances, and thiamine deficiency [21]. Treatment of uremic encephalopathy is based on improvement of the uremic state and appropriate adjustment, if possible, of renally metabolized/excreted medications.

Pancreatic Encephalopathy

The term “pancreatic encephalopathy” was coined in 1941 to describe the known association between acute pancreatitis and a severe diffuse encephalopathy [22]. Since then a number of reports further defined this syndrome [23–25].

Pancreatic encephalopathy typically occurs within 2 weeks of pancreatitis onset, especially between the second and fifth days, with varying incidences (up to as high as 35%) reported [1].

The diagnosis of pancreatic encephalopathy should be considered in any patient with a diffuse encephalopathy occurring in the setting of acute pancreatitis. Other than the laboratory findings diagnostic of pancreatitis, no specific laboratory or imaging feature is diagnostic of pancreatic encephalopathy; however, one report described severe diffuse white matter abnormalities on MRI in a patient with this syndrome [26].

Treatment consists solely of management of the pancreatitis; there is no specific neurologic treatment beyond supportive care and avoidance of benzodiazepines, which may worsen the encephalopathy. Neurologic improvement typically parallels the patient’s systemic recovery; however, the mortality rate for patients with pancreatic encephalopathy is high [1].

The pathogenesis of pancreatic encephalopathy is unknown but has been proposed to relate to blood-brain barrier breakdown as a consequence of activation of phospholipase A and conversion of lecithin into its hemolytic form [23], although fat embolism (described below) is another putative mechanism. Patients with pancreatitis are also at risk for the development of Wernicke’s encephalopathy, which should strongly be considered in the differential diagnosis or as an additional comorbidity in these patients [27].

Fat Embolism

Fat embolism should be considered among the potential emergent diagnoses of any patient presenting with a diffuse encephalopathy in characteristic clinical settings, such as after recent orthopedic procedures or trauma. The fat embolism syndrome is characterized by the classic clinical triad of encephalopathy, pulmonary dysfunction, and a petechial rash [28]. Although most commonly associated with long-bone trauma, fat embolism also occurs in a variety of other scenarios, including acute pancreatitis, diabetes mellitus, burns, joint reconstruction, liposuction, cardiopulmonary bypass, decompression sickness, and parenteral lipid infusion [29].

Clinical symptoms of fat embolism typically, though not invariably, occur 24–48 h after the inciting event [28].

The primary neurologic manifestation of fat embolism is a diffuse encephalopathy, although focal neurologic signs and seizures can occur. In some patients, the neurologic manifestations may be the sole clinical feature; however, pulmonary symptoms are typically present, and these symptoms may range from mild dyspnea to tachypnea to respiratory failure [30]. The finding of petechiae on the skin completes the clinical triad, but this is seen in only about 50% of patients with the syndrome. MRI in some patients has shown multifocal punctate DWI-positive white matter lesions consistent with multifocal embolic lesions and sometimes described as a *starfield pattern* [31, 32].

Two major mechanisms have been proposed to explain fat embolism syndrome. The mechanical theory proposes that bone marrow contents enter the lungs via the venous system, where they may also gain access to the systemic circulation and enter the brain via pulmonary arteriovenous shunts or a patent foramen ovale. The biochemical theory proposes that pulmonary abnormalities result from a toxic effect of circulating free fatty acids on lung cells; these theories are not mutually exclusive, and both mechanisms may be responsible for various aspects of the clinical syndrome [29].

The possibility of fat embolism should be considered in any patient with encephalopathy occurring in the appropriate clinical context, especially if other causes have been excluded. Treatment is currently supportive and focused on pulmonary management [28, 33].

Medication-Related Encephalopathy

Encephalopathy due to medications with central nervous system effects, including sedatives, analgesics, anticholinergics, anticonvulsants, anxiolytics, and any of the wide variety of CNS-active drugs, is well recognized. However, several medications in clinical use are particularly associated with specific and distinctive toxic encephalopathic syndromes and will be discussed here.

These medications are not uncommonly used, and neurologists in clinical practice are likely to be asked to consult on patients with encephalopathy due to one of these agents. Recognition of these unusual encephalopathic syndromes is important in the management of these patients to avoid unnecessary interventions (other than discontinuation or reduction of the offending agent) and possibly for consideration of specific antidotal therapy, such as for ifosfamide encephalopathy. Metronidazole, a commonly used antibiotic, which is also associated with an encephalopathic syndrome, is discussed in the next section on encephalopathies associated with distinctive imaging findings.

Ifosfamide

Ifosfamide, a chemotherapeutic agent used in the treatment of a variety of solid tumors, has been associated with the development of a severe encephalopathy [34]. Ifosfamide encephalopathy typically develops 24–48 h after infusion but may occur later. Encephalopathic symptoms due to ifosfamide may range from mild to severe and progress to coma and death. In addition, a distinctive catatonic-like, severely abulic state with mutism can be seen in patients with ifosfamide encephalopathy. Risk factors for ifosfamide encephalopathy include previous exposure to cisplatin, and concomitant opioids and CYP2B6 inhibitors, as well as abnormal laboratory findings, including low serum albumin, increased serum creatinine, and increased hemoglobin [35]. Due to theoretical considerations regarding the presumptive mechanism of ifosfamide encephalopathy from its metabolite chloroacetaldehyde, methylene blue, an electron acceptor, emerged as antidotal (and anecdotal) intravenous treatment of severe cases of this syndrome [36–38] although not based on controlled trials. Mild cases, however, typically resolve within days after stopping the agent. Due to similarities to Wernicke's encephalopathy, thiamine treatment has also been advocated for management of this syndrome [39, 40].

Cefepime

Many antibiotics have been associated with the development of an encephalopathy [41]; however, cefepime, a fourth-generation cephalosporin,

rin used to treat a variety of severe bacterial infections, is much more commonly associated with an encephalopathy than the other cephalosporins [42], manifested by progressive confusion and agitation which can progress to coma [43, 44]. Although cefepime encephalopathy was initially reported in patients with renal failure causing reduced clearance of the drug, cefepime encephalopathy also occurs in patients with normal renal function [45, 46]. In some patients with cefepime encephalopathy, EEG has shown non-convulsive status epilepticus [47, 48].

Management involves discontinuation of cefepime if possible, which leads to gradual resolution of the encephalopathy. In patients with nonconvulsive status epilepticus due to cefepime (or other cephalosporins) neurotoxicity, several reports have described short-term use of anticonvulsants in addition to discontinuation of the cephalosporin [47, 48], although it is unclear as to whether anticonvulsant therapy contributed to improvement.

Encephalopathies Diagnosed Primarily by Brain Imaging Findings

Findings on neuroimaging play an integral role in the timely recognition of several specific encephalopathic conditions, including the posterior reversible encephalopathy syndrome (PRES) and metronidazole encephalopathy; in addition, the finding of a splenial lesion on MRI, although non-specific, has been associated with various causes of encephalopathy. The imaging findings and clinical syndromes discussed in this section are in distinction to some of the encephalopathic syndromes discussed earlier, where the imaging findings are not specific or sensitive for an encephalopathy (e.g., T1 high signal in the basal ganglia in patients with chronic hepatic disease with or without encephalopathy) or they represent late findings that play little if any role in clinical diagnosis and emergent empiric therapy (e.g., the MRI findings in Wernicke's encephalopathy).

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome is a very common clinical syndrome, although

despite its descriptive name it does not always involve posterior brain regions and is not always completely reversible. Posterior reversible encephalopathy syndrome typically presents clinically with encephalopathy and visual disturbances (due to cortical visual dysfunction), and often also with seizures, and usually in association with elevated systemic blood pressure. The classic imaging finding is hyperintensity on T2-weighted and fluid attenuated inversion recovery (FLAIR) MRI consistent with vasogenic edema, typically predominantly involving the posterior occipital white matter; however, more diffuse involvement (including the brainstem and anterior hemispheres) can also be seen [49]. The predisposing conditions for the development of this syndrome are multiple, although common underlying systemic factors include eclampsia, hypertension with acute kidney disease, and exposure to various chemotherapeutic and immunosuppressive medications. The cause of PRES remains unclear, but the two main putative mechanisms include vascular leakage and vasogenic edema due to (1) elevated blood pressure above the autoregulatory limit and/or (2) as a result of toxin-related endothelial dysfunction [50]. Treatment includes blood pressure control, withdrawal or reduction of the potentially offending agent, and management of seizures if present. Prompt recognition and management of this syndrome should decrease the likelihood of permanent sequelae of this usually reversible condition [51].

Metronidazole Encephalopathy

Metronidazole is a commonly utilized antibiotic that is associated with an uncommon but characteristic toxic encephalopathy manifested primarily by confusion, dysarthria, and ataxia. MRI findings typical of metronidazole encephalopathy include T2 and FLAIR high-signal lesions involving the dentate nuclei [52]; additional involvement of the corpus callosum and deep hemispheric white matter and hypertrophy of the inferior olives have also been described [53, 54]. The clinical and radiographic findings of metronidazole-induced encephalopathy are usually reversible with discontinuation of the antibiotic, although severe persistent sequelae can

occur [55]. The syndrome of metronidazole encephalopathy may be more common in patients with hepatic or renal disease [56].

Splenic High-Signal Lesion

The MRI finding of an ovoid or round lesion within the splenium of the corpus callosum (high signal on FLAIR/T2 and often also on DWI) has been described as a nonspecific finding associated with a variety of encephalopathic syndromes, including those due to various metabolic disorders, viral infections (termed “encephalitis/encephalopathy”), and the use of, or withdrawal from, antiepileptic agents [57, 58]. This nonspecific clinical/imaging syndrome has come to be known as *mild encephalitis/encephalopathy with reversible splenic lesion* and has been divided into Type 1, characterized by the classic single lesion in the splenium of the corpus callosum, and Type 2, which includes lesions elsewhere in the white matter or anterior corpus callosum [59].

Patients with this imaging finding may have nonspecific encephalopathic symptoms including drowsiness, confusion, and agitation. Splenic high-signal lesions typically resolve on follow-up imaging in parallel with the patient’s clinical resolution. Although nonspecific, this MRI finding can nonetheless be a useful finding supportive of a probable reversible metabolic (or viral) encephalopathic syndrome and, despite its usual DWI positivity, should not be confused with an ischemic process affecting the corpus callosum.

Treatment of Patients with Encephalopathy

Treatment of some of the various specific encephalopathic syndromes has been discussed within the individual sections above. A general approach to management of the encephalopathic patient is, however, reviewed here.

As discussed at the beginning of this chapter, initial evaluation and treatment of the encephalopathic patient should focus on keeping a strong clinical suspicion for those causes of encephalopathy that will lead to irreversible neurologic dysfunction if not recognized and reversed immediately. Therefore, the immediate approach

to treatment of any encephalopathic patient includes correction of any circulatory deficiency and replacement of any potentially deficient metabolic substrate (e.g., oxygen, thiamine, or glucose). This should be followed by correction of any other potentially causative metabolic abnormality, management of any underlying causative acute systemic illness or complication of organ failure, and attempt at discontinuation or removal of any likely offending medication or toxin.

Since toxic-metabolic encephalopathies are due, by definition, to an underlying systemic process or medication (even if not yet diagnosed in the individual patient), management should focus on diagnosis and treatment of systemic dysfunction and removal of potential offending agents while attempting to minimize any CNS-active or sedating medications which might complicate or worsen the encephalopathy. For the same reason, it should not be surprising that a 2016 meta-analysis found that the use of antipsychotics in patients with delirium was not associated with change in duration or severity of delirium or hospital or ICU length of stay [60].

Conclusion

Neurologists are frequently asked to evaluate patients with encephalopathies. As reviewed in this chapter, in many cases a specific etiological diagnosis can be made through history, examination, laboratory studies, and, in some cases, imaging, which may lead to a specific medical intervention and more rapid clinical resolution and help prevent irreversible neurologic dysfunction. Physicians should approach each patient with encephalopathy with an especially high level of suspicion for those causes which may lead to incomplete neurologic recovery if not specifically and expeditiously diagnosed and treated. Clinicians should also recognize that patients with toxic-metabolic encephalopathy are inherently systemically critically ill and require emergent diagnosis and management of the underlying medical disorder or reduction or removal of the potentially offending substance.

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