VII ANOXIC, METABOLIC, AND TOXIC ENCEPHALOPATHIES

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The term encephalopathy is generally used to designate diffuse cerebral dysfunction. Such dysfunction is typically manifested by alterations in cortical function and disturbances of consciousness, ranging from mild confusional states (i.e., obtundation) to coma.[1] Abnormalities of consciousness reflect dysfunction of both cerebral hemispheres or of the reticular activating system in the brain stem. Encephalopathies may also be characterized by focal deficits, reflecting more localized cerebral dysfunction. In general, however, the cause is usually a systemic disorder that affects the brain diffusely, though some regions are more severely affected than others. A variety of mechanisms may contribute to encephalopathies, but anoxic, metabolic, and toxic factors are often significant and can lead to secondary structural abnormalities of the brain. Because of the risk of brain damage or death, diagnostic evaluation in patients with an encephalopathy of uncertain cause should proceed concurrently with stabilization and, in patients with acute coma of unknown cause, empirical treatment for common precipitating factors [*see Table 1*].

Clinical Evaluation

Metabolic and toxic encephalopathies cannot be distinguished with confidence from those caused by a mass lesion, but certain general points can be made. Onset is often insidious except when an acute event, such as cardiac arrest or drug overdose, is responsible. In general, the neurologic findings are symmetrical or multifocal in distribution, and tremor, asterixis, and myoclonus are common. Asterixis (sometimes referred to as a flapping tremor) consists of brief lapses of a sustained muscular contraction, as when the arms are held outstretched against gravity. Focal or lateralizing signs are absent or inconsistent; when present, they sometimes alternate from one side to the other. With some exceptions, preserved pupillary responses in the context of impaired brain stem function are strongly suggestive of metabolic or toxic disorders.

HISTORY

Evaluation requires an accurate history to determine the cause of the encephalopathy and the prognosis for recovery. It is important to determine whether the neurologic symptoms came on abruptly (as with vascular pathology) or gradually, whether the symptoms have progressed since their onset, and whether they were preceded by other symptoms and signs that may suggest the cause of the dysfunction. Generalized seizures occur in drug and alcohol withdrawal states, with various other toxic and metabolic encephalopathies, and in the presence of structural lesions of the brain. Partial seizures are more suggestive of focal pathology but may occur in certain metabolic disorders, especially when the disorder is superimposed on a preexisting focal structural lesion, such as an old stroke. Similarly, the past medical history should be reviewed in detail. A history or clinical features indicative of diabetes suggest that the obtundation is associated with iatrogenic hypoglycemia or a nonketotic hyperosmolar state, whereas the cause of obtundation in an alcoholic patient may be a metabolic disorder (e.g., hepatic disease or thiamine deficiency), toxicity (e.g., ethanol intoxication or withdrawal), an infection, or trauma.

PHYSICAL EXAMINATION

The general physical examination of encephalopathic patients is important. Jaundice, petechial hemorrhages, GI bleeding, ascites, or hypothermia may indicate hepatic dysfunction. A coarse facies, dry hair, or bradycardia suggests hypothyroidism. Acne, obesity, and hypertension are common in Cushing syndrome. Needle tracks in the skin raise the possibility of a toxic encephalopathy. Hypertension suggests that the encephalopathy is caused by a metabolic disorder (e.g., renal or endocrinologic) or ischemic disorder (e.g., cerebrovascular or cardiovascular), and hypothermia suggests a metabolic or toxic cause. Individual signs may be misleading, however, and must be evaluated within their clinical context; for example, fever and tachycardia are common signs of infection but also occur in drug and alcohol withdrawal states.

NEUROLOGIC EXAMINATION

The neurologic examination should characterize the nature and severity of the encephalopathy and should exclude a primary disorder of the central nervous system. An encephalopathy associated with signs of meningeal irritation suggests meningitis or subarachnoid hemorrhage, whereas a focal neurologic deficit or evidence of increased intracranial pressure mandates exclusion of an intracranial mass lesion. In metabolic or toxic encephalopathies, focal or lateralizing neurologic signs are often absent, but their presence does not exclude such disorders.

In determining the nature and severity of an encephalopathy,

Table 1 Immediate Management of Patients with an Encephalopathy of Uncertain Cause

- Maintain adequacy of respiration and circulation
- Obtain blood samples for determination of the following:
  - Serum glucose and electrolytes
  - Complete blood count and sedimentation rate
  - Liver and kidney function studies
  - Toxicity screen
- Obtain urine for toxicity screen
- For coma of acute onset and unknown cause, administer the following:
  - Dextrose, 25 g I.V. (to treat possible hypoglycemia)
  - Thiamine, 100 mg I.V. (to prevent or treat Wernicke encephalopathy)
  - Naloxone, 1 mg I.V. (to treat possible opiate overdose)
- General clinical and neurologic examination
- Computed tomographic scanning of the head (if focal intracranial lesion is suspected)
- Lumbar puncture (if meningitis or subarachnoid hemorrhage is suspected)
- Arterial blood gas determinations (to distinguish between different causes of metabolic encephalopathy)
- Chest radiography
- Further investigation and treatment, depending on results of initial studies

the mental status is evaluated with particular regard to the level of consciousness as judged by the attention span and response to verbal or painful stimuli [*see Table 2*]. Orientation, behavior, language function, mood and affect, thought content, and memory should also be assessed, if possible. Brief examination of the CNS requires evaluation of the cranial nerves, especially the pupillary responses, and of sensorimotor functions in the limbs, including tendon reflexes and plantar responses.

Although pupillary responses to light are often normal in persons with metabolic and toxic encephalopathies, a variety of pupillary abnormalities may occur. For example, fixed dilated or poorly responsive pupils often result from acute cerebral anoxia or intoxication with anticholinergic or sympathomimetic agents; depending on the circumstances in which they are encountered, such pupillary responses should also raise concern about a herniating intracranial mass lesion. Pinpoint pupils are a feature of opioid toxicity, organophosphate poisoning, or use of miotic eyedrops; they are also a common sequela of pontine damage, as from a stroke. Abnormal asymmetry of pupil size or responsiveness suggests that a structural brain stem (or cranial nerve) lesion is responsible; such symptoms are unlikely in metabolic and toxic encephalopathies. Reflex ocular movements should also be assessed. In comatose patients, loss of oculovestibular responses may occur with either a structural pontine lesion or sedative intoxication. By contrast, downward deviation of one or both eyes with unilateral cold-water stimulation strongly suggests sedative intoxication.

As an encephalopathy becomes progressively more severe, patients become comatose. The depth of coma is best characterized by the response to external stimulation [*see Table 2*]. Lateralized responses suggest a structural lesion, whereas bilaterally symmetrical responses occur with either structural or metabolic-toxic pathology. In cases of expanding or progressive structural lesions causing downward transtentorial herniation, loss of cortical function may occur in a rostrocaudal sequence [*see Table 2*].

Table 2 Evaluation of Level of Consciousness

Level of Consciousness	*Characteristics*
Confusional state	Patient is disoriented, is irritable, and has a poor attention span Hallucinations and delusions may occur
Stupor	Patient is inattentive, drowsy, and unresponsive but can be aroused by vigorous stimuli for short periods
Coma	Patient is unresponsive and unarousable In patients with downward transtentorial herniation, the level of dysfunction is further characterized (below)
Diencephalic level	Reactive pupils Preserved oculocephalic responses
Early	Purposive response to pain
Late	Decorticate response to pain
Midbrain level	Fixed and midsized pupils Abnormal oculocephalic responses Decerebrate response to pain
Lower brain stem level	Fixed and midsized pupils Abnormal oculocephalic responses No response of upper limbs to pain

Anoxic Encephalopathies

CARDIAC DISORDERS

Circulatory Arrest

Transient circulatory arrest may lead to global cerebral ischemia and thus to syncope, sometimes preceded by nonspecific premonitory symptoms such as paresthesias, light-headedness, palpitations, and graying-out of vision. Syncope is associated with pallor and loss of muscle tone, but prolonged ischemia results in tonic posturing, sometimes accompanied by irregular jerking movements that resemble seizures. If postictal confusion occurs, it clears within 1 minute. In elderly patients, syncope may present simply as unexplained falls. Syncope may be related to cardiac pathology, dysautonomia, postural hypotension, endocrinopathies, and metabolic disorders. Neurocardiogenic (vasovagal) syncope, however, is the most common variety [*see 1:1 Approach to the Cardiovascular Patient*].

Depending on its duration, ventricular fibrillation or asystole may cause irreversible anoxic-ischemic brain damage. The prognosis varies with the patient's age, the duration of circulatory arrest, and the interval before cardiopulmonary resuscitation and defibrillating procedures were undertaken. Circulatory arrest from ventricular fibrillation has a better prognosis than that from asystole. The neurologic consequences of the arrest may relate to the accumulation of intracellular calcium, increased extracellular concentrations of glutamate and aspartate, and increased levels of free radicals.

In the mature nervous system, gray matter is generally more vulnerable to ischemia than white matter, and the cerebral cortex is more sensitive than the brain stem. So-called watershed areas bordering the zones supplied by major arteries are especially vulnerable.

Circulatory arrest of less than 5 minutes' duration leads to transient confusion or temporary loss of consciousness and impaired cognitive function. Complete recovery is usual, but in rare instances, the circulatory arrest is followed after 7 to 10 days by a demyelinating encephalopathy, with increasing cognitive dysfunction and pyramidal or extrapyramidal deficits that may have a fatal outcome. In such cases, patients regain consciousness several hours after the circulatory arrest but then develop progressive neurologic deficits, such as intellectual deterioration; personality changes; seizures; cortical blindness; amnestic syndromes; or, less commonly, the locked-in syndrome (characterized by quadriplegia and mutism), extrapyramidal syndromes, bibrachial paresis, or intention (action) myoclonus. Spinal cord dysfunction may occur but is unusual.

Circulatory arrest of longer than 5 minutes' duration may cause widespread and irreversible brain damage, resulting in prolonged coma. Prognosis for survival or useful recovery is poor, especially when brain stem reflexes (most notably the pupillary responses to light) are lost. In particular, loss of pupillary reactivity for more than 24 hours or persistence of coma for more than 4 days indicates a poor prognosis. In one study, comatose survivors of cardiac arrest who continued to have nonreactive pupils, failed to open their eyes in response to pain, or had absent or reflex motor responses 3 days after onset of coma generally failed to survive or to regain useful independent function [*see Table 3*].[2] In this study, the most accurate single predictor of poor outcome immediately after restoration of spontaneous circulation was the absence of pupillary response to light: Outcome was poor (i.e., death or persistent vegetative state) in 73 of 89 pa-

tients (82%) with absent pupillary responses.[2] Even if consciousness is regained, focal or multifocal neurologic signs may lead to significant disability from focal motor deficits, extrapyramidal disturbances (e.g., parkinsonism), sensory loss, seizures, myoclonus, and disturbances of higher cortical function from which recovery is usually delayed and incomplete. Intention (action) myoclonus is particularly characteristic in such circumstances; it is often activated by startle or various sensory stimuli and is responsive only occasionally to clonazepam, valproate, piracetam, or 5-hydroxytryptophan. The last two medications are not commercially available in the United States.

Some patients never fully regain consciousness after circulatory arrest, remaining in a persistent vegetative state or showing evidence of brain death. The persistent vegetative state is characterized by the return of sleep-wake cycles and of various reflex activities, but wakefulness is without awareness.[3,4] Recent studies have indicated (1) that the minimally conscious state, which is characterized by inconsistent but clearly discernible behavior of consciousness, can be distinguished from coma and a vegetative state by the presence of behavioral conditions not found in either of those two conditions; (2) that this distinction is important because outcome appears to be different in minimally conscious patients; and (3) that the minimally conscious state may be transient or permanent.[5]

Brain death is defined as the loss of all cerebral activity, including activity of the cerebral cortex and brain stem, for at least 6 hours if confirmed by electroencephalographic evidence of electrocerebral inactivity or for 24 hours without a confirmatory electroencephalogram. A useful clinical test in patients with suspected brain death is the apnea test. This test involves evaluation of the respiratory response of the brain stem by allowing the carbon dioxide tension (P_{CO_2}) to rise to 60 mm Hg while 100% oxygen is given through the endotracheal tube. Brain-dead patients have no ventilatory response to the apnea test.

Brain death may be simulated clinically by extreme hypothermia, sedative overdose, and neuromuscular blockade. Such conditions must always be excluded, especially when no clear history of circulatory arrest can be obtained.

Disorders Associated with Cardiac Procedures

Cardiac catheterization or percutaneous transluminal coronary angioplasty sometimes causes cerebral emboli that may lead to focal neurologic deficits or an encephalopathy manifested by a behavioral disturbance. Encephalopathy, seizures, and cerebral infarction after cardiac surgery usually result from hypoxia or emboli. Postoperative encephalopathies may also relate to metabolic disturbances, medication, infection (especially in immunosuppressed patients), or multiple organ dysfunction syndrome (MODS). Postoperative seizures may result from focal or generalized cerebral ischemia, electrolyte or metabolic disturbances, or MODS. Recognition of the precise cause of encephalopathy in such cases can be difficult. After cardiopulmonary bypass is performed, intracranial hemorrhage may result because of diminished platelet adhesiveness and reduced levels of coagulation factors.

Table 3 Clinical Evaluation of Prognosis in Comatose Survivors of Cardiac Arrest

Sign	*Patients with Poor Outcome (%)*		
	Immediate	*Day 3*	*Day 7*
Lack of response to pain			
No opening of the eyes	69	100	100
No motor response	75	100	100
Lack of response to verbal stimuli	67	94	100
Lack of pupillary response	83	100	100

Coronary angioplasty leads to cerebral emboli in approximately 1% of cases, but when undertaken after acute myocardial infarction, it is associated with a higher risk of stroke and anoxic encephalopathy.[6]

An encephalopathy may occur soon after cardiac transplantation as a side effect of an immunosuppressive agent or as the result of an infection (e.g., meningitis, meningoencephalitis, or cerebral abscess) related to immunosuppressive therapy. Infecting organisms include *Aspergillus, Toxoplasma, Cryptococcus, Candida, Nocardia,* and viruses. In patients on long-term immunosuppressive agents, an encephalopathy may develop from a primary CNS lymphoma [*see 11: VI Neoplastic Disorders*].

The occurrence of an encephalopathy after coronary artery bypass surgery may be caused by stroke, which develops in about 2% to 4% of bypass patients[7] and is either embolic or, less commonly, the result of watershed infarction from hypoperfusion. Risk factors include advanced age, proximal aortic atherosclerosis, hypertension, previous stroke or transient ischemic attack (TIA), and diabetes.[8] A carotid bruit or radiologic evidence of atherosclerosis of the carotid artery does not clearly increase the risk of stroke, and carotid endarterectomy before cardiac surgery is of questionable utility.[9]

In rare cases, patients do not recover consciousness after surgery, and no specific metabolic cause can be identified. This encephalopathy is probably the result of diffuse cerebral ischemia or hypoxia. Hemispheric or multifocal infarction is sometimes responsible.

Metabolic Encephalopathies

RESPIRATORY DISEASES

Hypoxia and Hypercapnia

The pathogenesis of neurologic abnormalities related to hypoxia and hypercapnia is not fully understood, because hypoxia is often associated with acid-base imbalance and leads to hematologic and biochemical changes that affect cerebral function. Moreover, both hypercapnia and hypoxemia can result from impaired ventilation, and their neurologic sequelae are not easily differentiated.

Chronic pulmonary insufficiency leads to an encephalopathy characterized by headache, confusion, disorientation, and impaired cognitive function. Examination may also reveal a postural tremor, myoclonus, asterixis, and hyperreflexia; papilledema is sometimes present. These findings are not only the result of cerebral hypoxia but also the result of hypercapnia, which produces cerebral vasodilatation, increased cerebrospinal fluid pressure, and an altered pH of the CSF.

High-altitude sickness can lead to an encephalopathy characterized by headache, fatigue, anorexia, nausea, poor concentration, and sleep disturbances.[10] Symptoms of high-altitude sickness begin within hours or days of ascent to altitudes above

10,000 ft. In severe cases or at higher altitudes, consciousness is impaired and coma may occur—sometimes with a fatal outcome. Cerebral edema causes papilledema, retinal hemorrhages, cranial neuropathies, a variety of sensorimotor deficits, and behavioral disturbances. The basis of high-altitude sickness is unknown,[11] but glucocorticoids may prevent or relieve symptoms [*see 14:X Pulmonary Edema*].

Hypocapnia

Hypocapnia, which results from hyperventilation, causes cerebral vasoconstriction, a decline in the peripheral availability of oxygen, and an altered ionic balance of calcium. The resultant encephalopathy leads to light-headedness, paresthesias, visual disturbances, headache, unsteadiness, tremor, nausea, palpitations, and loss of consciousness. Muscle cramps and carpopedal spasms also occur. The many causes of hyperventilation include hepatic coma, brain stem lesions, and certain cardiopulmonary diseases, but in many instances, no specific cause can be found.

SEPSIS

A diffuse encephalopathy with progressive obtundation may complicate sepsis, especially in patients with acute respiratory distress syndrome. The cause of sepsis-related encephalopathies is uncertain but may relate to cerebral edema, hypoxia, disruption of the blood-brain barrier, direct cerebral infection, toxins produced by organisms infecting other tissues, alterations in the cerebral microcirculation, metabolic disturbances, and the effects of medications.[12] Sepsis-related encephalopathy tends to be worse at night, is associated with marked EEG abnormalities, and often clears spontaneously. Overt infection should be treated vigorously, metabolic abnormalities should be corrected, and medication requirements should be reviewed.

LIVER DISEASE

Portosystemic Encephalopathy

Encephalopathy can result from chronic liver disease and sometimes precedes systemic features of hepatic dysfunction [*see 4:IX Cirrhosis of the Liver*]. It may be precipitated by GI hemorrhage, a high protein intake, use of certain sedatives and diuretics, or sepsis. Portosystemic encephalopathy is characterized by a fluctuatingly abnormal mental status, often with an insidious onset that delays clinical recognition of the disorder. Somnolence, obtundation, and agitation can occur and may progress to coma. Ocular reflexes are preserved, but disconjugate eye movements or tonic ocular deviation (downward) may be found in rare instances. A flapping tremor (asterixis) is often conspicuous; in severe cases, decerebrate or decorticate posturing, hyperreflexia, and bilateral extensor plantar responses may be present. Routine liver function tests may not correlate with the severity of the encephalopathy. The fasting arterial ammonia concentration and EEG findings of diffuse slow activity with associated triphasic waves are more helpful in determining severity. Respiratory alkalosis is commonly present. The CSF often shows nonspecific abnormalities, but an increased glutamine level is strongly supportive of hepatic encephalopathy. Abnormal signal intensities may be found in the basal ganglia on T_1-weighted magnetic resonance imaging.

The mechanism of portosystemic encephalopathy is unknown. Treatment consists of reduction of hyperammonemia,[13] restriction of dietary protein intake; control of GI bleeding; management of portal hypertension; removal of blood from the GI tract; administration of lactulose or neomycin; correction of associated electrolyte, biochemical, and hematologic disturbances; and general supportive measures [*see 4:XIII Enteral and Parenteral Nutritional Support*].

Chronic Non-Wilsonian Hepatocerebral Degeneration

Some patients with chronic liver disease develop a permanent neurologic deficit resembling that of Wilson disease, with action (intention) tremor, ataxia, dysarthria, and choreoathetosis. Severity correlates best with the fasting arterial ammonia level. Neuroimaging studies may be abnormal. There is no specific treatment.

Liver Transplantation

An encephalopathy that worsens soon after liver transplantation suggests organ rejection, cerebral anoxia, or a complication of immunosuppressive agents, especially cyclosporine. Seizures often occur, suggesting metabolic disturbances, cerebrovascular disease, infections, or medication complications. Encephalopathies occurring weeks or months after liver transplantation are usually caused by infections or malignancies involving the nervous system.

PANCREATIC ENCEPHALOPATHY

Acute pancreatitis has been associated with a transient encephalopathy, but its symptoms are nonspecific and resemble those of other metabolic encephalopathies. Diagnosis, therefore, hinges on exclusion of other metabolic causes.

GASTROINTESTINAL DISEASES

Nutritional deficiency is the usual cause of any neurologic complication of GI disorders, but it is usually impossible to determine the responsible nutrient. Neurologic complications occur in up to 15% of patients who undergo gastric resection. Vitamin B_{12} absorption is impaired because of loss of gastric intrinsic factor; impaired vitamin B_{12} absorption can lead to a variety of disturbances [*see 5:III Anemia: Production Defects*]. Gastric plication has been associated with a nonspecific encephalopathy, myelopathy, polyneuropathy, Wernicke encephalopathy, and a nutritional amblyopia, but the responsible nutritional deficiencies are unknown. Chronic gluten enteropathy causes a progressive and sometimes fatal CNS disorder, with some combination of encephalopathy, myelopathy, cerebellar disturbances, and peripheral neuropathy.

RENAL FAILURE

Uremic encephalopathy clinically resembles other metabolic encephalopathies, and its severity cannot be related to any single laboratory abnormality. Its pathophysiologic basis remains uncertain,[14] but it is usually attributed to the accumulation of toxic organic acids in the CNS or to the direct toxic effects of parathyroid hormone.

Dialysis Disequilibrium Syndrome

The dialysis disequilibrium syndrome consists of an encephalopathy characterized by headache, irritability, agitation, somnolence, seizures, muscle cramps, and nausea. It occurs during or after hemodialysis or peritoneal dialysis and has been related to shifting of water to the brain. Other features of dialysis disequilibrium syndrome include exophthalmos, increased intraocular and intracranial pressure, and papilledema.

Dialysis Dementia

In some patients who have undergone dialysis for more than a year, a fatal encephalopathy called dialysis dementia has developed. The cause of this condition is uncertain, although aluminum intoxication has been suggested as the cause, for two reasons: (1) increased cerebral concentrations of aluminum are found at postmortem examination and (2) dialysis dementia has become rare since aluminum was removed from dialysates.[15] A characteristic early feature is hesitancy of speech, followed by speech arrest. As the disorder advances, intellectual function declines, and hallucination, delusions, seizures, myoclonus, asterixis, gait disturbances, and other neurologic abnormalities develop. Death usually occurs within 1 year after onset. Deferoxamine, a chelating agent that binds aluminum, is often prescribed, but the optimal duration of treatment is unknown. Deferoxamine therapy may exacerbate encephalopathy in patients with high serum aluminum levels[16] and may provoke visual and auditory disturbances.[17]

Renal Transplantation

The long-term immunosuppressive treatment in patients who undergo renal transplantation can lead to encephalopathic complications.

ELECTROLYTE DISTURBANCES

Sodium

Hyponatremia and hypernatremia have several causes [*see 10:I Renal Function and Disorders of Water and Sodium Balance*]. Rapid changes in serum sodium concentration can cause encephalopathy because the osmotic equilibrium between the CSF and other body fluids is altered. Disturbances of cognition and arousal occur and may lead to coma. Associated features include myoclonus, asterixis, tremulousness, and seizures. Seizures are often poorly responsive to anticonvulsant medication unless the associated metabolic disturbance has been corrected. Focal motor deficits (e.g., hemiparesis) can occur with hyponatremia in the absence of any structural lesion or with hypernatremia as a result of intracerebral or subdural hemorrhage related to osmotically caused brain shrinkage, with secondary tearing of blood vessels.

In patients with acute brain syndromes, such as subarachnoid hemorrhage, hyponatremia is often erroneously attributed to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). In such patients, hyponatremia is more often caused by salt wasting than by SIADH; because plasma volume is reduced, fluid restriction exacerbates hypovolemia and can result in cerebral ischemia. Hyponatremia should be corrected at a rate not exceeding 12 mEq/L/day because rapid correction of hyponatremia leads to central pontine myelinolysis [*see* Nutritional Deficiencies, *below*].[18] Central pontine myelinolysis may obscure or follow improvement in hyponatremic encephalopathy. When severe, it leads to obtundation, a spastic or flaccid quadriparesis, and pseudobulbar palsy; in mild cases, clinical deficits are minimal, though conspicuous abnormalities may be detectable on MRI.

Potassium

Alterations of serum potassium concentration can have several causes [*see 10:II Disorders of Acid-Base and Potassium Balance*]. Hyperkalemia usually causes disturbances of cardiac rhythm before affecting neurologic function, but occasionally the arrhythmia is accompanied by burning paresthesias, progressive flaccid paralysis, depressed tendon reflexes, and mental changes. Treatment depends on the underlying cause, the severity of the electrolyte disturbance, and the electrocardiographic findings. Hypokalemia usually causes reversible neuromuscular dysfunction rather than an encephalopathy.

Calcium

The main CNS complication of hypercalcemia is an encephalopathy characterized by an impaired level of consciousness, headache, apathy or agitation, and, in rare cases, seizures. Neuromuscular complications (e.g., muscle weakness and fatigability) result from involvement of the peripheral nervous system.

Tetany is a widely recognized manifestation of hypocalcemia, but focal or generalized seizures can also occur, as can an encephalopathy characterized by confusion, hallucinations, delusions, psychosis, disturbances of consciousness, and cognitive impairment. The seizures are resistant to anticonvulsant drugs until the hypocalcemia is corrected. Other CNS complications include parkinsonism and chorea that clear with correction of the serum calcium level; increased intracranial pressure and a myelopathy may also occur with hypocalcemia.

Magnesium

Hypomagnesemia may coexist with hypocalcemia and has similar neurologic complications. Hypermagnesemia leads to an encephalopathy with drowsiness, confusion, diminished responsiveness, and depressed or absent tendon reflexes. Hypotension, respiratory depression, and weakness from impaired neuromuscular transmission may also be present. In severe cases, coma ensues, with the possibility of a fatal outcome.

PITUITARY DISEASE

Encephalopathy is common in Cushing disease, which leads to a variety of symptoms, including anxiety, agitation, insomnia, depression, euphoria, excitement, and psychoses. Intracranial hypertension, with its attendant effects on cerebral function, may complicate Cushing syndrome; it occurs particularly after resection of the pituitary adenoma.

Hypopituitarism leads to apathy and intellectual decline, but the specific hormonal basis of these symptoms is uncertain because several hormones are affected concurrently.

Diabetes insipidus leads to an encephalopathy that ranges in severity from irritability to somnolence to coma. Patients are hypotensive and hyperthermic. Vasopressin or a long-acting vasopressin analogue is the usual therapeutic approach.

THYROID DISEASE

Hyperthyroidism

An encephalopathy that is common in hyperthyroidism takes the form of anxiety, restlessness, tremulousness, irritability, emotional lability, poor concentration, headaches, and insomnia. Depression and lethargy may be conspicuous in elderly patients (i.e., apathetic hyperthyroidism). Seizures can occur. Examination commonly reveals a postural tremor and generalized hyperreflexia. Chorea and paroxysmal choreoathetosis have also been described.

A more severe encephalopathic disturbance characterizes thyrotoxic crisis, with confusion and agitation progressing to coma. Thyrotoxic crisis is often associated with fever, cardiac arrhythmias, and other systemic disturbances. It is treated with hydrating and cooling agents, beta blockers, glucocorticoids, and occasionally plasmapheresis [*see 3:I Thyroid*].

Hypothyroidism

Mental changes are often seen in cases of hypothyroidism. Apathy, somnolence, and poor concentration are often attributed to depression. Cognitive function may decline. Confusion, delirium, and psychosis also occur. Symptoms reverse with correction of the thyroid disorder. Severe hypothyroidism may lead to impairment of consciousness accompanied by hypotension, hypothermia, respiratory failure, hypoglycemia, and other metabolic abnormalities. If treatment is delayed, the encephalopathy progresses to coma, sometimes with a fatal outcome.

Hashimoto Thyroiditis

A relapsing encephalopathy manifested by confusion, alterations in consciousness, seizures, tremulousness, and myoclonus may develop in patients with Hashimoto thyroiditis. Strokelike episodes of deterioration are common. Investigations reveal a diffusely abnormal EEG and an increased CSF protein concentration without associated pleocytosis, but neuroimaging studies show no abnormalities other than a patchy uptake on isotope brain scan. The disorder is treated with glucocorticoids and is associated with a good long-term prognosis.[19]

DIABETES MELLITUS

An encephalopathy may occur in diabetic patients as a consequence of metabolic derangements directly related to the diabetes or its treatment or to complications of the disease, such as renal failure (see above). It may also be related to cerebrovascular disease, which is relatively common in diabetic patients, who have an increased incidence of hypertension and atherosclerosis.

Diabetic ketoacidosis may be the presenting feature of previously unrecognized diabetes. Clinical presentation is with an encephalopathy—in this case, an altered state of consciousness that progresses from mild confusion to coma. If there is no underlying structural disease of the brain, there are usually no focal or lateralizing signs. The encephalopathy is probably multifactorial. Serum hyperosmolality, acidosis, and disseminated intravascular coagulation (DIC) are likely contributing factors of importance; other metabolic derangements, infection, vascular occlusive phenomena, and cerebral edema may also be involved. Treatment is with fluid and electrolyte replacement and I.V. insulin (10 to 20 units given as a bolus, followed by continuous infusion of 10 to 15 U/hr in normal saline, with the dose being lowered as the blood glucose level declines) [*see 9:VI Diabetes Mellitus*].

Nonketotic hyperosmolar coma typically occurs in elderly patients with mild diabetes [*see 9:VI Diabetes Mellitus*]. Progressive obtundation is the predominant clinical manifestation, sometimes accompanied by seizures and focal deficits. Hypotension and evidence of dehydration may be present. Treatment involves fluid replacement with hypotonic (one-half normal) saline, correction of hyperglycemia with I.V. insulin, and correction of other biochemical derangements.

HYPOGLYCEMIA

Hypoglycemia causes an acute metabolic encephalopathy that can lead to irreversible brain damage if treatment is delayed. The most common cause of the hypoglycemia is insulin administration in diabetic patients [*see 9:VI Diabetes Mellitus*]; other causes include hepatic disease, alcoholism, and various tumors [*see 9:I Hypoglycemia*]. Hypoglycemia leads initially to sweating, tachycardia, dilated pupils, tremulousness, and mental changes, which, depending on the level of the hypoglycemia, may include anxiety, confusion, stupor, or coma. The warning signs of sympathetic overactivity may not be evident in patients with autonomic dysfunction. As the depth of coma increases, the plantar responses become extensor, and decorticate or decerebrate posturing occurs. Brain stem dysfunction (including abnormal pupillary responses) and transitory focal neurologic deficits—sometimes alternating from side to side—may also occur. In some patients, seizures may be the only manifestation of hypoglycemia. Depressed respiration, heart rate, and tendon reflexes presage the development of irreversible brain damage. Administration of glucose improves or reverses symptoms and signs within a few minutes and should not be delayed for laboratory confirmation of hypoglycemia. All patients presenting with an encephalopathy of uncertain cause should therefore immediately receive 50 ml of 50% dextrose I.V.

NUTRITIONAL DEFICIENCIES

Wernicke Encephalopathy

Wernicke encephalopathy is common in alcoholic patients. It also occurs in malnourished patients (especially when glucose or oral hypoglycemic agents are administered), in patients on kidney dialysis, in obese patients treated with gastroplasty, and in patients who vomit persistently. Thiamine (vitamin B_1) deficiency is responsible for the hallmark features of Wernicke encephalopathy, which include ophthalmoplegia (nystagmus, extraocular palsies, gaze palsies, and, in rare cases, internuclear ophthalmoplegia), gait ataxia, and fluctuating confusional states. Pathologic changes occur in characteristic regions of the brain stem, especially in the mamillary bodies and thalamus. Diffusion-weighted MRI may show signal changes in these characteristic midline locations.[20] A polyneuropathy is often present, and hypothalamic involvement may lead to hypotension and hypothermia. The prognosis depends on the rapid initiation of effective therapy. Treatment is by thiamine replacement (100 mg I.V. daily for 1 week, followed by daily oral supplementation). Improvement of the ophthalmoplegia commences within a day or so, and improvement of the encephalopathy is seen in days to weeks, but residual deficits are common.

Korsakoff Encephalopathy

As with Wernicke encephalopathy, Korsakoff encephalopathy is attributed to thiamine deficiency, though the precise pathophysiology is unknown. Selective disturbance of memory is the predominant clinical abnormality, but thiamine replacement therapy rarely leads to improvement. There is marked impairment of recent memory and difficulty in incorporating new memories, though immediate recall is intact. Patients are unaware of any deficit and often confabulate. Other cognitive abnormalities are found less often. The disorder is common in chronic alcoholics, often occurring in association with Wernicke encephalopathy (Wernicke-Korsakoff syndrome). The pathologic changes are similar in distribution to those in Wernicke encephalopathy (see above).

Subacute Necrotizing Encephalomyelopathy

Subacute necrotizing encephalomyelopathy occurs as an autosomal recessive disorder in children (rarely in adults). The distribution of pathologic changes of this disorder resembles that of Wernicke disease, suggesting that the disorder relates to a disturbance of thiamine metabolism. Thiamine supplementation is sometimes helpful, but the encephalomyelopathy is not caused by nutritional deficiencies alone, and its precise pathophysiolog-

ic basis is unclear. Symptoms and signs include cognitive decline, seizures, flaccid weakness, optic atrophy, nystagmus, ataxia, vomiting, and irregular respirations. Death often results within a few months. There is no specific treatment.

Pellagra

Deficiency of niacin (nicotinic acid) leads to an encephalopathy in addition to cutaneous lesions, glossitis, anemia, and GI disturbances (e.g., anorexia, nausea, and diarrhea). Poor concentration, irritability, and affective complaints are followed by confusion, hallucinations, delusions, and pyramidal and extrapyramidal deficits (e.g., tremor and rigidity). A polyneuropathy may also occur. Pathologic changes are widespread in the CNS but most commonly involve Betz cells in the motor cortex. The response to treatment with niacin is usually disappointing, which suggests that other nutritional deficiencies may be involved.[21]

Central Pontine Myelinolysis

Central pontine myelinolysis is manifested clinically by confusion or more marked impairment of consciousness, pseudobulbar palsy, pyramidal deficits in the lower extremities or all extremities, and extensor plantar responses. Symptoms and signs progress over days to weeks; locked-in syndrome or coma may occur in advanced cases. The pathologic hallmark of the disorder is breakdown and loss of myelin in the anterior pons and other brain stem regions, which may be visualized by MRI.[22] The disorder is associated with alcoholism, electrolyte disturbances, malignant disease, and malnutrition, and it relates particularly to the rapid correction of hyponatremia. For this reason, hyponatremia should generally be corrected by no more than 12 mEq/L/day [*see* Electrolyte Disturbances, *above*].

Vitamin B_{12} Deficiency

Encephalopathy is a well-recognized complication of vitamin B_{12} deficiency. It may be accompanied by myelopathy, optic neuropathy, and peripheral neuropathy, either alone or in any combination. The neurologic complications do not reflect the presence or the severity of any associated megaloblastic anemia. Folic acid masks the hematologic abnormality and fails to prevent the neurologic complications. Thus, fortification of the food supply with folic acid, which began in 1994 in the United States, means that anemia may not be evidence of vitamin B_{12} deficiency in the future. Treatment with vitamin B_{12} arrests and may reverse the neurologic disorder; the extent of any residual deficit relates to the severity and duration of symptoms before initiation of treatment[23] [*see 5:III Anemia: Production Defects*].

Hyperalimentation

An encephalopathy may occur in patients receiving parenteral hyperalimentation, usually because of metabolic abnormalities such as hypophosphatemia, hyperammonemia, or hyperosmolarity. A malignant form of Wernicke encephalopathy (see above) may develop if thiamine supplementation is not provided to patients who are being supported parenterally for prolonged periods.

Toxic Encephalopathies

IATROGENIC DISORDERS

Many toxic encephalopathies are iatrogenic in origin.[24] The CNS is affected by many drugs in a variety of ways, but the resultant disturbances of CNS function generally reverse with withdrawal of the offending medication. Attention here is directed at those medications that cause diffuse disturbances of cerebral function manifested particularly by alterations in the level of consciousness. Iatrogenic encephalopathies commonly manifest themselves primarily as seizures or as focal neurologic deficits, such as extrapyramidal and cerebellar syndromes.

Coma is a common sequela of overdosage with various drugs, including hypnotics, sedatives, neuroleptics, antidepressants, anticonvulsants, and analgesics. Clinical examination generally reveals pupil sparing (i.e., pupillary responses remain intact), though pinpoint pupils are found in opioid poisoning, and dilated, sluggish pupils occur with barbiturate or glutethimide overdose. Spontaneous and reflex ocular movements are typically impaired, even at an early stage, in barbiturate and phenytoin intoxication. Depending on the depth of coma, the corneal reflex may be lost, and painful stimuli to the trunk or extremities may lead to purposive movements, decorticate or decerebrate posturing, or absence of motor response. Flaccidity and hyporeflexia of the limbs are common, but spasticity, hyperreflexia, and extensor plantar responses are sometimes found.

A fluctuating level of consciousness—with confusion, delirium, hallucinations, and a poor attention span—may occur, especially in the elderly, in reaction to many medications, including various antimicrobials, CNS depressants, antiparkinsonian drugs, anticonvulsants, and cardiovascular agents. Nonspecific behavioral changes—such as restlessness, irritability, sleep disturbances, affective changes, and nightmares—often occur initially, but their significance may not be recognized. Examination often reveals tremor, asterixis, and myoclonus in addition to mental disturbances. Nystagmus may also be present, particularly when CNS depressant drugs or anticonvulsants have been taken. A similar clinical disturbance may result from withdrawal of certain medications, such as benzodiazepines or barbiturates.

Some encephalopathies may be related to the infectious and neoplastic complications associated with immunosuppressive and chemotherapeutic agents. Such agents and other drugs causing encephalopathies include cisplatin,[25] paclitaxel,[26] valproate,[27] vigabatrin,[28] cyclosporine,[24,29] methotrexate,[30,31] and cefuroxime.[32] Encephalopathies have been associated with transcatheter embolization[33] and allogeneic bone marrow transplantation,[34] and they may also occur as a direct consequence of treatment with glucocorticoids (e.g., causing behavioral disturbances and psychoses).[35] Among other medications prescribed for the treatment of cardiac disorders, lidocaine and related agents may cause seizures, tremor, paresthesias, and confusional states. Calcium channel blockers, beta blockers, digoxin, and thiazide diuretics can also cause encephalopathies.

ALCOHOL-RELATED DISORDERS

Alcohol intoxication leads initially to behavioral changes (e.g., disinhibition, irritability, euphoria), dysarthria, ataxia, nystagmus, tachycardia, and cutaneous flushing. Increased alcohol intake may cause obtundation, coma, hyporeflexia, respiratory depression, and death. Level of tolerance to alcohol may influence the behavioral response to a particular blood level of alcohol.

Acute withdrawal from alcohol after a period of regular consumption can lead initially to postural tremor and signs of autonomic hyperactivity. Seizures may also occur, especially within the first 48 hours after withdrawal. The seizures are usually generalized tonic-clonic convulsions that are self-limited and rarely require anticonvulsant drug treatment. Delirium tremens may

develop 2 to 7 days after withdrawal; it is characterized by marked agitation, excitement, hallucinations, hyperthermia, dehydration, and hypotension. Treatment is with benzodiazepines, fluid and electrolyte replacement, and general supportive measures [*see 13:III Alcohol Abuse and Dependency*].

Various encephalopathies can occur in alcoholics as a result of nutritional deficiencies (see above).

Miscellaneous Encephalopathies

DISSEMINATED INTRAVASCULAR COAGULATION

DIC may occur with diseases of the brain and other organs, septicemia, immune-mediated disorders, diabetic ketoacidosis, neoplastic disease, and obstetric complications [*see 5:XIII Hemorrhagic Disorders*]. The clinical manifestations of DIC, including the predominance of thrombosis or hemorrhage, are influenced by its cause, rate of onset, and severity. Encephalopathy is a common manifestation, ranging in severity from mild confusion to coma. Even comatose patients may recover fully; they therefore require continuing support.

CONNECTIVE TISSUE DISEASES AND VASCULITIDES

Connective tissue diseases are characterized by an autoimmune inflammatory response and vasculitis. The common direct CNS manifestations are encephalopathy with cognitive or behavioral changes and focal neurologic deficits. An encephalopathy may also result from metabolic disturbances related to the involvement of other organs or to treatment, such as with glucocorticoids and immunosuppressive agents.

Common features of direct CNS involvement in polyarteritis nodosa, allergic granulomatous angiitis (Churg-Strauss syndrome), and overlap syndrome include headache (sometimes indicative of an aseptic meningitis) and behavioral disturbances, such as cognitive decline, acute confusion, and affective or psychotic disorders. The EEG may be diffusely slow; neuroimaging studies are sometimes abnormal. Focal CNS deficits, which are uncommon, are usually caused by infarction or hemorrhage. Angiography may not reveal the vasculopathy.

Headache is the most common initial complaint of patients with giant cell (temporal) arteritis [*see 15:VIII Systemic Vasculitis Syndromes*]. Other features of giant cell arteritis include masticatory claudication and acute unilateral or bilateral blindness, which may be permanent. Other CNS complications are rare, but encephalopathy with neuropsychiatric disturbances, strokes, seizures, and other manifestations sometimes occurs in these patients.

In Wegener granulomatosis, cerebral involvement results from vasculitis or extension of granulomas from the upper respiratory tract.[36] The resulting encephalopathy may be caused by basilar meningitis with associated cranial neuropathies, temporal lobe dysfunction, cerebral infarction, or venous sinus obstruction.

Headache, cognitive deficits, behavioral and neuropsychiatric disturbances, and focal or multifocal deficits from small infarcts are usual presenting features of isolated angiitis of the CNS. Consciousness becomes depressed as the disease advances. The CSF exhibits a lymphocytic pleocytosis and increased protein concentration. Focal ischemic changes may be detected by computed tomography or MRI; angiography sometimes shows beading of vessels. Meningeal and brain biopsy is usually necessary to make a definitive diagnosis.

Rheumatoid arthritis, the most common of the connective tissue diseases, rarely causes encephalopathy unless involvement of the upper cervical spine or atlantoaxial dislocation causes headaches or hydrocephalus or leads to brain stem deficits from direct medullary compression or vertebral artery involvement.

In most patients with systemic lupus erythematosus, neurologic complications ultimately develop, often during the first year. Episodic affective or psychotic disorders are common and often difficult to distinguish from corticosteroid-related mental disturbances. Alterations in consciousness sometimes occur. Focal neurologic deficits may be manifestations of strokes related to cardiac valvular disease, the presence of antiphospholipid antibodies, or cerebral vasculitis.[37]

Generalized or partial seizures sometimes occur; they probably result from microinfarcts, metabolic disturbances, and systemic infections.

Neurologic complications are uncommon in Sjögren syndrome but may include encephalopathic features, such as behavioral and psychiatric disturbances, that may relate to aseptic meningitis, meningoencephalitis, or focal neurologic dysfunction. About 20% of patients with Behçet syndrome develop an aseptic meningitis or meningoencephalitis that leads to an encephalopathy. Focal or multifocal deficits may also result from cerebral ischemia. The CSF is commonly abnormal, with a mild pleocytosis and increased protein concentration.

Antiphospholipid antibodies (the lupus anticoagulant and anticardiolipin antibodies) are found especially in patients with certain connective tissue diseases,[38] in patients taking various medications, in patients with infections and obstetric complications, and as an incidental finding [*see 5:XIV Thrombotic Disorders*]. An acute ischemic encephalopathy, manifested by confusion, obtundation, quadriparesis, and bilateral pyramidal signs, has been described in patients with antiphospholipid antibodies.[39]

The pathogenesis of the thrombotic tendency associated with the presence of these antibodies is unclear. Immunosuppressive therapy is not indicated. Cerebral thrombosis is managed as it is in other contexts.

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Acknowledgments

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