

CHAPTER 22

NEUROLOGIC COMPLICATIONS OF SYSTEMIC DISEASES

INTRODUCTION

Systemic medical conditions may cause central and peripheral nervous system dysfunction. It is important to recognize that the function of all organ systems is to keep the brain alive. If treatment is initiated for systemic organ failure (i.e., medication, transplantation, surgery), these may be associated with other types of neurological disorders. Rather than memorizing lists of neurological disorders associated with specific systemic disorders, it is important to understand the mechanism of neurological dysfunction associated with systemic disease.

RENAL DISORDERS

Neurologic complications can be related directly to renal impairment or can result from treatment modalities dialysis, kidney transplant or immunosuppressive medication utilized for transplant. CNS dysfunction occurs when glomerular filtration rate declines below 10% of normal; however, no relationship exists between encephalopathy and blood urea nitrogen or serum creatinine level. Early encephalopathy symptoms include anorexia, nausea, hyperactivity, sleep disruption, and inattention. As renal function worsens, symptoms include vomiting, lethargy, impaired cognition, paranoia, and abnormal fatigue. In severe encephalopathy, symptoms include confusion, abnormal behavior, dysarthria, myoclonus, asterixis, and seizures. EEG shows diffuse slow pattern. Renal encephalopathy can be exacerbated by other metabolic abnormalities, for example, acidosis, hyperosmolarity, hyponatremia, and hypocalcemia. Seizures develop *late* in renal encephalopathy. If seizures occur, consider complicating pathological condition e.g. brain hemorrhage due to coagulation disorder, metabolic disorder, medication effect. Treatment of seizures with valproate, phenytoin, and phenobarbital requires careful monitoring because blood levels are usually low in uremic patients, but free drug levels can be high, low, or normal depending on protein binding changes.

Polyneuropathy occurs in two thirds of chronic renal failure patients. This cannot be distinguished from neuropathy caused by other metabolic conditions, for example, alcohol or diabetes mellitus. In chronic renal failure patients, “restless legs” syndrome, characterized by burning, prickling, crawling, and aching sensations in the legs, can develop. Following dialysis there is usually improvement in neuropathy, but this can worsen, especially in diabetic patients undergoing dialysis; however, renal transplant causes neuropathy remission.

Because of fluid and electrolyte shifts, neurologic disturbances develop in patients undergoing dialysis. The “disequilibrium syndrome” is characterized by headaches, nausea, cramps, altered mentation, and seizures. This develops within 24 hours postdialysis and usually spontaneously resolves; therefore, treatment of a single seizure immediately after dialysis is probably not warranted. Because renal failure patients have bleeding disorders, dialysis can precipitate intracranial bleeding such as subdural, subarachnoid or intracerebral hematomas. If

neurologic findings do not clear rapidly following dialysis, neurodiagnostic studies (e.g., EEG, CSF, and CT/MRI) are indicated; however, in most cases they are not necessary because clinical improvement develops within 48 hours of dialysis.

In renal failure patients who have undergone chronic hemodialysis, “dialysis dementia” can occur. This is characterized by speech disorders (e.g., dysarthria, dyspraxia, stuttering, mutism), seizures, or motor disturbances. EEG findings consist of bilateral spike and wave complexes and bursts of diffuse slow waves. Epileptic causes of these EEG abnormalities are possible and rarely improve with AED; clinical course is usually progressive deterioration. Aluminum, contained in dialysate, has been found in high levels in gray matter of these patients and has been suggested as a possible etiologic agent; however, other trace elements have also been implicated. By deionization of dialysate water, trace elements are removed, and incidence of “dialysis dementia” lowered. It is important to exclude other metabolic conditions (hypercalcemia, Wernicke’s syndrome with thiamine deficiency, hyponatremia, drug effect) or structural neurologic conditions (subdural hematoma, stroke, infectious-inflammatory disorders, and lymphomas) as cause of dementia. Neurological complications caused by immunosuppressive medication also occur.

DIABETES MELLITUS

Neurologic complications of diabetes mellitus include accelerated atherosclerotic disease involving large or small blood vessels to cause strokes; encephalopathy because of metabolic abnormalities such as hypoglycemia, ketoacidosis, and hyperosmolarity; retinopathy and visual loss; neuropathy. The most common neurological complication is neuropathy. This is a complex clinical syndrome, which affects multiple portions of peripheral nervous system (symmetrical sensorimotor polyneuropathy, autonomic neuropathy, polyradiculopathy, cranial mononeuropathy, amyotrophy, focal mononeuropathy). Patients with early, uncontrolled hyperglycemia may report uncomfortable sensory symptoms in their feet and legs. Nerve conduction velocities are slowed. With establishment of tight glucose control, those symptoms disappear. In some diabetic patients who have no clinical neuropathy symptoms electrophysiological abnormalities indicate asymptomatic neuropathy; however, it is not known if, these patients are at risk of developing clinical neuropathy. Polyneuropathy usually develops slowly, with initial sensory disturbances in distal extremities. Patients report aching or cramping pain and paresthesias, which are most severe nocturnally. Clinical findings in diabetic neuropathy include absent ankle jerks and impaired vibration sense on soles of feet; distal motor weakness is less frequent. If there is proprioceptive dysfunction, neuropathic ulcers and joint deformity (Charcot joints) develop. It is important to differentiate vascular from neuropathic ulcers because treatment differs. Foot and leg pain, which is most intense at night, is neuropathic; if worse with walking, consider vascular etiology. The course of neuropathy is variable; some patients spontaneously improve and others show progressive impairment. After having diabetes for 25 years, more than 50% of patients have neuropathy. The mechanism of neuropathy is believed due to accumulation of abnormal metabolites with metabolic and vascular (nerve hypoxia) dysfunction impairing mitochondrial activity. Tight diabetic control with normalization of blood sugar has major effect in preventing microvascular complication, including neuropathy. Major features of neuropathy include anesthesia and pain. Anesthesia

may lead to foot ulcers and infection; careful diabetic foot care is mandatory. Neuropathic pain control should be initiated if it interferes with patient activities and sleep.

Diabetic mononeuropathy can involve any nerve(s). Onset is sudden. Frequently pain is the initial symptoms, followed by motor dysfunction. Functional recovery develops several weeks to months later, consistent with vascular causes with pathologic evidence of infarction in the vasa nervorum of peripheral nerve. The most frequently involved nerves are the femoral and sciatic in lower extremities -- the median and ulnar in upper extremities. Sudden onset of paresthesias in the lateral thigh (lateral femoral cutaneous nerve) is characteristic of meralgia paresthetica. Cranial nerves (especially facial and extraocular) are frequently involved. If there is sudden onset of painful unilateral oculomotor paresis, diagnosis of a ruptured posterior communicating artery aneurysm should be suspected; however, in diabetic oculomotor paresis, pupil is spared; angiography is not necessary and clinical recovery occurs spontaneously. Diabetic amyotrophy is characterized by asymmetrical proximal pelvic girdle weakness. There are dysesthesias in the anterior thighs without objective sensory loss. These patients appear cachectic (wasted) and have significant weight loss. The EMG and muscle biopsy findings are consistent with neuropathic process. Diabetic amyotrophy patients frequently improve with rigorous blood sugar control. Autonomic dysfunction usually occurs in diabetic polyneuropathy. Clinical findings include orthostatic hypotension, impotence, intermittent nocturnal diarrhea, delayed gastric emptying, and atonic bladder causing urinary incontinence.

Central nervous system disorders such as impaired consciousness, seizures, or focal neurologic deficit can complicate hyperglycemia; however, also consider hypoglycemia due to medication effect (e.g., insulin, oral hypoglycemic agents). In patients with ketoacidosis, encephalopathy and generalized seizures can develop; however, in nonketotic, hyperosmolar, hyperglycemic states, focal seizures and lateralized neurologic deficit can occur more frequently. Potential mechanisms for this dysfunction in diabetic, nonketotic, hyperosmolar, hyperglycemic states include acidosis, ketosis, systemic hypotension, cerebral hypoxia, hyperosmolar condition, dehydration, and intravascular coagulation. Serum hyperosmolality causes water to move out of cells and shrink, and also causes endothelial cell dysfunction with injury to blood-brain barrier. Despite the presence of stroke-like syndromes, diagnostic and pathologic findings do not show vascular ischemia.

ALCOHOLISM

Alcoholism is a chronic disease. The patient drinks despite medical, neurologic (Box 22-1), psychiatric, social, economic, and legal contraindications. Alcohol has a specific effect on excitatory (glutamate) receptors and alters neuronal membrane lipids and proteins. Genetic factors may explain why certain alcoholic patients develop alcohol-related neurological impairment, and others do not. In acute intoxication, patients demonstrate impaired judgment, euphoria, poor coordination, slurring of speech, and socially inappropriate behavior. Brief episodes of memory "blackouts" can occur. Certain patients become agitated and combative and cause property or personal damage (pathologic intoxication); this can occur independently of amount of alcohol ingested. Stupor, coma, respiratory depression, and death can be precipitated by direct neurotoxic effect of alcohol or by other alcohol-related complications, for example, hypoglycemia, metabolic acidosis, hepatic encephalopathy, and subdural hematoma. Respiratory

depression can occur when mixing alcohol with sedatives. The correlation between blood alcohol level and intoxication severity is a function of alcohol tolerance and duration of alcohol exposure. For example, chronic alcoholics can tolerate blood alcohol levels of 400 mg/dl, whereas nonalcoholics can be severely affected by this blood alcohol level.

Symptoms of alcohol withdrawal occur in patients who have been drinking constantly and suddenly stop because there is a lack of money to purchase more alcohol or intercurrent illness develops and makes alcohol intake painful (e.g., gastritis). Initial symptoms include tremulousness, nervousness, insomnia, hyperirritability, hypervigilance, nightmares, auditory, visual, or tactile hallucinations; these improve after patients have a drink. If patients remain abstinent, symptoms can persist for 7 to 14 days. Seizures can develop 6 to 48 hours after the last drink; in fact, seizures can be more delayed after cessation of alcohol intake if other CNS depressant medications are used. Seizures are generalized major motor in type. They are usually single or consist of brief seizure clusters. The EEG is usually normal, with the exception of spikes or slow waves in postictal period. EEG can show photomyoclonic or photoconvulsive response. Not all alcohol withdrawal seizures are benign! Five percent are status epilepticus. Because most alcohol withdrawal seizures are self-limited, anticonvulsant treatment is not always needed. For the prevention of recurrent seizures related to alcohol, lorazepam is more effective than phenytoin. Lorazepam has more prolonged effect than diazepam with minimal depressant effect on cardiovascular and respiratory system. Prophylactic anticonvulsant treatment is not indicated after acute hospitalization episode; alcoholic patients frequently discontinue their medications especially when drinking heavily. These give two reasons for seizures to occur. The toxic effect of alcohol and abrupt anticonvulsant cessation would lower the seizure threshold to cause clinical seizures. Delirium tremens is most likely to occur in patients who have had withdrawal seizures.

Mild withdrawal symptoms (enhanced generalized physiological tremor with autonomic hyperactivity including pronounced arousal response, tachycardia, sweating, hyper-reflexia) becomes prominent 24-hours after drinking stops and can be managed by fluid replacement and placement of patient in quiet supportive environment with reorientation utilizing one-to-one contact without need for medication. Acute delirium tremens develop 3 to 5 days following cessation of drinking. It is characterized by acute confusion, tremulousness, motor restlessness, and autonomic hyperactivity (tachycardia, hypertension, sweating, fever, papillary dilatation). This is usually self-limited, lasting several days; however, it is sometimes more prolonged (as long as 2 weeks) and associated with mortality if complicated by infection, Wernicke's syndrome, or cardiomyopathy. Treatment of acute delirium tremens includes four vital components (Box 22-2). With more severe symptoms including autonomic hyperactivity, utilize benzodiazepines. If medication is required, short acting medications with fewer active metabolites are preferred especially in elderly patients and those patients with hepatic impairment. Beta-adrenergic antagonists are utilized if benzodiazepines do not control autonomic hyperactivity. If severe agitation and hallucinations occur, anti-psychotics can be utilized with caution as they may cause cardiovascular depression.

Nutrition-related neurologic disorders include Wernicke-Korsakoff syndrome. Patients with this syndrome have altered mentation, unsteady ataxic gait, and eye movement disorders. Because these patients are confused and inattentive, memory function cannot be adequately tested. The patient's stumbling gait is related to neuropathy in association with vestibular and cerebellar dysfunction. Abnormal eye findings include abducens paresis, lateral gaze palsy,

horizontal or vertical nystagmus. Pathologic lesions characterized by petechial hemorrhagic and diffuse microscopic necrotic lesions are seen in mammillary bodies, hypothalamus, and thalamus.

As confusional state resolves, Wernicke's syndrome patients can show amnestic (Korsakoff's) syndrome. These patients appear apathetic and dull but can demonstrate entertaining (confabulation) response to mental questioning. Treatment of Wernicke-Korsakoff syndrome includes thiamine (100 mg parenterally initially with daily oral multivitamins). Administration of glucose-containing fluids without thiamine can exacerbate neurologic deficit and precipitate cardiovascular collapse in Wernicke's syndrome patients.

Alcoholic-related cerebellar degeneration develops frequently in poorly nourished patients. Pathologic findings are cerebellar cortex and anterior vermis degeneration. These patients have broad-based ataxic gait with impaired heel-to-shin movements and relatively intact finger-to-nose movements. Clinical course can show progressive worsening or stabilization; deterioration usually occurs during a subsequent drinking period. If patients become abstinent and maintain good nutritional status, improvement occurs. In alcoholics, neuropathy frequently develops. In some cases, paresthesias are intense, and patients cannot tolerate pressure of bed sheets on the feet. Amblyopia with centrocecal scotoma is frequently caused by nutritional optic atrophy.

Other neurologic conditions of undetermined cause include: acute necrotizing myopathy (alcohol has direct cytotoxic effect on muscle) characterized by muscle pain, tenderness, and proximal weakness; central pontine myelinolysis, characterized by quadriplegia, mutism, bulbar involvement, and eye movement abnormalities with pathologic evidence of focal brainstem demyelination visualized by CT or MRI; Marchiafava-Bignami syndrome, characterized by dementia, seizures, rigidity, aphasia, and urinary incontinence and demyelination involving anterior corpus callosum; and cerebral atrophy and dementia with ventricular and subarachnoid space dilatation. Brain atrophy can normalize (reverse) with abstinence, hydration, and protein repletion.

Alcohol consumption increases the risk of ischemic and hemorrhagic (stroke). Mechanisms for hemorrhagic stroke include bone marrow suppression with thrombocytopenia, coagulation disorders due to impaired production of hepatic factors, development of acute autonomic hyperactivity with severe hypertension. Alcohol may be protective for ischemic stroke with low intake (one to two drinks per day) due to enhanced fibrinolysis, elevated prostacyclin and positive effects on lipid metabolism; whereas at higher intake level it may cause hypercoagulable and dyslipidemic effects.

HEPATIC DISORDERS

Hepatic encephalopathy (also referred to as portal systemic encephalopathy) characterized by altered mentation and abnormal motor function (e.g., tremor, asterixis, myoclonus) develops in patients with hepatic dysfunction. There is reversible cerebral dysfunction associated with hepatic impairment and portal hypertension with shunts diverting hepatic portal blood into systemic circulation. The most characteristic finding is "liver flap" or asterixis. There is sudden wrist flexion when wrist is dorsiflexed and fingers are extended. There is sudden, rapid palmar flapping movement followed by slow return to original dorsiflexed

wrist position. Asterixis is best stimulated by examiner pushing against patient's outstretched wrist. Asterixis can spread to feet or tongue. It is seen in conscious patients, but disappears as consciousness deteriorates. Asterixis is seen most commonly in hepatic disease but also in renal or pulmonary encephalopathies. Patients with hepatic encephalopathy can be mildly confused or more severely impaired (coma). Some hepatic encephalopathy patients are delirious with asterixis and tremor to simulate delirium tremens. Severity of hepatic encephalopathy correlates with elevated free flowing (no use of tourniquet) blood ammonia level, although role of other brain neurotransmitters (glutamate, gamma-aminobutyric acid, organic thio-alcohols, short-chain fatty acids) must be considered. EEG shows diffuse slowing with superimposed paroxysmal triphasic delta waves. Because patients with hepatic impairment are predisposed to trauma-related and infectious-inflammatory neurologic conditions, CT, MRI, and CSF examinations can be indicated if there are atypical or focal neurological signs. In rare instances, patients with hepatic dysfunction develop neurologic deficit including dyskinesia caused by non-Wilsonian hepatolenticular degeneration and spastic paraparesis caused by cortical or spinal cord degeneration. Pathologic findings in patients who have hepatic encephalopathy include abnormal astrocytes (Alzheimer type II) visualized in the cerebral cortex, putamen, globus pallidus, thalamus, and cerebellum. MRI shows hyperintense lesions in the globus pallidus on T-1 images and these regress following successful treatment. Treatment of hepatic encephalopathy includes correction of underlying hepatic disorder and metabolic abnormalities, oral lactulose (to reduce ammonia levels) in doses of 20 to 30 grams four times daily, and protein restriction. Neomycin treatment (2 to 3 grams daily) has been replaced by lactulose because neomycin has auditory-vestibular and renal toxicity.

In patients with acute liver failure (viral hepatitis, toxin exposure, acetaminophen ingestion, Reye syndrome), cerebral edema may develop. These patients develop reduced level of consciousness and seizures. CT/MRI may show compression of ventricles and subarachnoid spaces as markers of cerebral edema. Utilization of intracranial pressure monitoring devices and treatment of intracranial hypertension may prevent hypoxic-ischemic brain injury as these patients await liver transplantation.

FLUID AND ELECTROLYTE DISORDERS

Water Intoxication and Hyponatremia

Electrolyte disturbances occur in medical and surgical patients to cause central and peripheral (nerve, neuromuscular transmission, and muscle) neurological disorder. Sodium affects CNS; potassium affects muscle to cause weakness. Magnesium and calcium affect both central and peripheral nervous system.

Hyponatremia can occur if water intake exceeds urinary excretion; this results in decreased plasma osmolality, increased intracellular and extracellular water, and possibly cerebral edema, herniation syndromes, and ultimately death. Hyponatremia is associated with hypo-osmolality and there are three types (hypo-, normo-, and hypervolemic). In water intoxication, there can be brain swelling with expansion and flattening of cerebral gyral pattern and narrowing of sulcal spaces. There is swelling of astrocytes, especially in white matter. This condition can result from excess secretion of vasopressin (syndrome of inappropriate anti-

diuretic hormone or SIADH). It can also occur in patients with CNS diseases including head trauma, meningitis, and postoperative neurosurgical (hypothalamic-pituitary) procedures. Other causes for hyponatremia include compulsive (psychogenic) water drinking, Addison's disease, and renal disease with defective water excretion. In hyponatremic patients, diagnosis of SIADH is established when serum osmolality is paradoxically low when compared to urine osmolality. Neurologic manifestations of hyponatremia include mental confusion, muscle cramps, weakness, and seizures. Certain patients are asymptomatic despite marked hyponatremia, if hyponatremia develops gradually; others are comatose with recurrent seizures if hyponatremia and low serum osmolality develops rapidly. Correct with hypertonic (3 percent saline at 4 to 6 ml/kg) saline. When hyponatremia is overcorrected (more than 12 mEq/L per day), central pontine myelinolysis may occur. Clinical features include spastic quadriparesis, pseudobulbar palsy and other signs of pontine dysfunction. MRI show large areas of hyperintensity in the central pontine region. Because of the potential risk of this disorder, never overcorrect hyponatremia rapidly.

Treatment of hyponatremia consists of fluid restriction or administration of hypertonic saline. If status epilepticus develops as result of hyponatremia, treatment with intravenous hypertonic saline infusion may be necessary. Hyponatremic volume expanded patients (congestive heart failure, nephrotic syndrome) should be fluid restricted. If hyponatremia is caused by endocrine disorders such as adrenal insufficiency or hypothyroidism, treatment of these conditions should correct hyponatremia. Certain medications can cause hyponatremia by interfering with patient's ability to excrete water (e.g., oral hypoglycemics, antipsychotics, antiepileptics, narcotics, sedatives, anti-neoplastic drugs). Withdrawal of causal medication is necessary. Neurological symptoms of hyponatremia are more common with acute rather than slow fall of serum sodium. These patients with slowly falling sodium can have an underlying neoplasm or chronic respiratory disease. Hyponatremia caused by SIADH can also be corrected with lithium or demeclocycline.

Hypernatremia

Hypernatremia most commonly occurs in infants and elderly patients with serum sodium levels exceeding 160 mEq/L. Hypernatremia results from water loss producing sodium excess, such as sweating and vomiting. This usually occurs in patients with impaired thirst mechanism, decreased fluid intake, diabetes insipidus, or as consequence of osmotic diuresis. It is most common in dehydrated infants or elderly patients who do not receive adequate fluid replacement. Neurologic findings include altered mentation, increase in muscle tone (rigidity and opisthotonos), and seizures. There is extracellular hyperosmolarity and intracellular dehydration with brain shrinking. In hypernatremic infants, rapid fluid shifts can cause intracranial hemorrhage or hypercoagulable condition predisposing to cerebral infarction. Treatment includes rehydration with plasma expanders. This must be performed carefully to avoid intracellular edema and signs of water intoxication. During treatment of hypernatremia, prevent severe hypotension by using isotonic colloid solutions, monitoring blood pH to avoid acidosis, replacing fluids using hypotonic fluid, and treating underlying cause of hypernatremia.

Hypocalcemia

Hypocalcaemia results from low oral intake, high intestinal loss, malabsorption, vitamin

D deficiency, high urinary loss, or hypoparathyroidism. It is most common following thyroid and parathyroid surgery. Calcium is necessary for neuronal membrane stability. Hypocalcemia results in CNS hyperexcitability (seizures, mental change), peripheral and cranial nerves irritability (tetany, laryngeal stridor, paresthesia, muscle cramps, spasms), and cardiac conduction system abnormalities (prolonged Q-T interval). Clinical features of hypocalcemia are exacerbated by hyperventilation, hypomagnesaemia, and alkalosis. The cardinal findings of acute hypocalcemia are tetany (intermittent tonic muscle contractions). This is manifested by twitching of face and mouth muscles in response to tapping over the facial nerve (Chvostek's sign) and carpopedal spasm that is spontaneous or develops in response to inflating a blood pressure cuff between systolic and diastolic levels for three minutes (Trousseau sign). Neurologic findings caused by chronic hypocalcemia include papilledema, cataracts, parkinsonism, mental retardation, and basal ganglia calcification. For acute hypocalcemia, parenteral therapy consists of 1 or 2 ampules (containing 90 mg calcium/ampule) administered intravenously in 15-minute intervals to prevent seizures, laryngospasm, and death. Treatment of chronic hypocalcemia includes oral calcium gluconate and vitamin D.

Hypercalcemia

Primary hyperparathyroidism with production and release of excess parathyroid hormone can result from parathyroid hyperplasia, adenoma, or carcinoma. Other causes of hypercalcemia include sarcoidosis, metastatic carcinoma, multiple myeloma, prolonged immobilization. It causes reduced neuromuscular excitation with resultant muscle weakness and fatigue. Other clinical manifestations include headaches, irritability, depression, anxiety, abdominal pain, constipation, polydipsia, polyuria, encephalopathy, myopathy, and polyneuropathy. Treatment depends on the specific cause of hypercalcemia.

Hypokalemia

Hypokalemia can result from renal tubular necrosis or adrenal (hyperaldosteronism) dysfunction, mineralocorticoid drugs, diuretic therapy, vomiting, or diarrhea. It is most common electrolyte disorder. Neurologic symptoms include weakness, which can be episodic and does not occur until potassium concentration falls below 3 mEq/L. Findings include hyporeflexia and proximal muscle weakness; this can cause bulbar and respiratory dysfunction. Episodic (lasting 30 minutes to several days) paralysis can occur with minor changes in extracellular fluid; this is characteristic of familial periodic paralysis (FPP). Episodic weakness can develop with either hypokalemia or hyperkalemia. FPP is transmitted as an autosomal dominant traits. In hypokalemic FPP attacks can be precipitated by high carbohydrate diet, sodium intake, diuretics, diarrhea, and rest after vigorous exercise.

Hyperkalemia

Cardiac rhythm disturbances occur prior to development of neuro-muscular disturbances. Etiology includes renal and adrenal (Addison) insufficiency, acidosis prior to or following insulin therapy. Muscle weakness is cardinal neurological symptom.

Hypophosphatemia

This disorder develops in patients receiving hyperalimentation, malnourished hospitalized patients, alcoholics, and patients with respiratory alkalosis and diabetic ketoacidosis. Neurologic dysfunction includes encephalopathy, ataxia, seizures, asterixis, dyskinesias, ptosis, dysphagia, dysphonia, and respiratory dysfunction caused by muscle weakness. Also, neuropathy simulating Guillain-Barré syndrome can develop. Patients at risk for hypophosphatemia should receive phosphorus-containing food (skim or low-fat milk) or phosphorus supplementation. Phosphorus deficiency can increase magnesium excretion to cause hypomagnesemia. This can exacerbate muscle weakness with reduced deep tendon reflexes.

Hypomagnesemia

The American diet is magnesium deficient. Magnesium depletion occurs from reduced intake and absorption and increased renal loss. Neurological features include hyperirritability – seizures, tremor, myoclonus hyperreflexia, and tetany; therefore, symptoms may simulate hypocalcemia.

Hypermagnesemia

This is uncommon except in patients who receive magnesium sulfate for treatment of eclampsia of pregnancy. Early symptoms are loss of deep tendon reflexes. At higher levels CNS depression and reduced respiratory drive and muscle paralysis may occur. Paralysis is due to neuro-muscular transmission abnormality.

ENDOCRINE CONDITIONS

Hyperthyroidism

Patients with hyperthyroidism have CNS dysfunction (hyperkinesias, anxiety, insomnia, mood swings, and postural tremor), ophthalmoplegia, myelopathy, or muscle disorders (myopathy or myasthenia gravis). Some disturbances are caused by sympathetic (adrenergic) hypersensitivity and respond to treatment with β -adrenergic blocking agents (propranolol). Myopathy improves when patients become euthyroid. Myasthenia gravis can exacerbate or remit when patients become euthyroid. Neurological disorders may result from hormonal dysfunction or immune-mediated mechanisms (see Hashimoto encephalopathy). Hypokalemic periodic paralysis can exacerbate in thyrotoxic patients and resolve in the euthyroid state.

Ophthalmologic findings of adrenergic hypersensitivity include upper lid retraction, lid lag, widened palpebral fissures, and infrequent blinking. These resolve following restoration of euthyroid condition and respond to treatment with β -blocking agents. Other eye findings caused by infiltrative ophthalmopathy include muscle restriction (especially on superior or lateral gaze), exophthalmos, corneal ulceration, and decreased visual acuity. Exophthalmos is usually bilateral; however, if findings are asymmetrical, this can simulate orbital mass. Radiologic

studies (orbital ultrasound, CT/MRI) may be necessary to exclude orbital mass. The relationship of thyroid hormone abnormalities to infiltrative ophthalmopathy is not clearly established. Ocular findings can develop in patients after successful medical thyroid treatment or surgical thyroidectomy. Ophthalmopathy can progress such that eyeball becomes immobile, vision is impaired, and corneal ulceration occurs. Corticosteroids are indicated if vision is threatened; orbital surgical decompression may be required to preserve vision.

Hypothyroidism

In adults myxedema can cause psychomotor retardation, confusion, dementia, psychoses (myxedema madness), peripheral neuropathy, myopathy, myasthenia gravis, cerebellar ataxia, abnormal reflexes with delayed relaxation phase and myoedema (mounding of muscles when directly percussed), or auditory-vestibular nerve impairment.

In myxedema patients, coma with severe hypothermia can be precipitated by sedative drugs (which depress respiration to cause carbon dioxide retention), infection, or trauma. Treatment consists of measures to control temperature regulation, corticosteroid (because of associated adrenal insufficiency), and gradual restoration of the thyroid hormone. Myxedema coma is a medical emergency. This requires treatment with intravenous triiodothyronine, which is biologically active thyroid hormone as well as corticosteroids medication.

Hashimoto Encephalopathy

In Hashimoto thyroiditis, antithyroid antibodies may be present even though the patient may remain euthyroid or become hypothyroid. There may be multiple systemic manifestation of immune-mediated disorder-pernicious anemia, rheumatoid arthritis, myasthenia gravis, SLE. Patients with Hashimoto encephalopathy may present with an encephalopathy and seizures or with focal deficit. Diagnosis is established by presence of one or more anti-thyroid antibodies. Treatment includes high dose corticosteroids. This is autoimmune encephalopathy but the role of anti-thyroid antibodies to neurological dysfunction is not established.

Excess Corticosteroid States

The most common cause is iatrogenic or endogenous (Cushing's syndrome of adrenal or hypothalamic origin). Hypercortisol states can cause behavioral effects (depression, euphoria, insomnia, mania) but also psychoses with suicidal ideation. Cognitive impairment and confusional states are less common. The incidence of psychoses can be less than 1% in patients receiving less than 40 mg of prednisone, but 20% in patients receiving 80 mg of prednisone. Clinical features usually include mania, sleep disorders, motor restlessness and agitation. Systemic side effects of excess corticosteroids include peptic ulceration, hypertension, enhanced fat production, enhanced capillary fragility, lymphopenia, impaired immunologic response, and protein catabolism. Daily corticosteroid treatment is more likely to cause psychoses than alternate-day therapy. Other adverse effects of corticosteroid excess included: papilledema which is caused by idiopathic intracranial hypertension; weakness because of myopathy; spinal cord or nerve root dysfunction relating to spinal compression by epidural fat; spinal compression due to fracture as a result of osteoporosis; visual impairment as a result of glaucoma or cataract

formation; porosis; visual impairment as a result of glaucoma or cataract formation; and impaired ocular motility disorder caused by enlarged retro-orbital fat.

Corticosteroid Insufficiency

Primary adrenal gland insufficiency (Addison's disease) is the most common cause of corticosteroid insufficiency. Neurologic manifestations include behavioral effects such as abnormal fatigue, lethargy, apathy, or cognitive inefficiency. These patients are extremely sensitive to low doses of CNS drugs (hypnotics), which can cause encephalopathy. In patients with adrenal insufficiency, consider adrenoleukodystrophy, which is dysmyelinating white matter disorder, especially in boys.

Hypoglycemia

Neurologic symptoms do not usually develop unless the blood sugar concentration is less than 40 mg/dl. The most common causes of hypoglycemia are insulin therapy for diabetes mellitus and alcoholism with acute fatty liver and reduced hepatic glycogen. Hypoglycemic symptoms may be of two types – those related to sympathetic nervous system hyperactivity and those related to inadequate glucose delivery to the brain. Those related to autonomic hyperactivity include tremulousness, palpitation, diaphoresis, anxiety, hunger; those related to reduced brain sugar content includes dizziness, confusion, headache, difficulty speaking, loss of consciousness, seizure, and weakness. Neurologic symptoms include paresthesias, blurred vision, diplopia, slurred speech, and confusion; with severe hypoglycemia, syncope, Babinski signs, seizures, and even coma with impaired brainstem reflexes (absent caloric response with preserved papillary reactivity) can occur. Consider hypoglycemia as a possible cause in patients with anxiety neurosis of recent onset, episodic unresponsiveness, or status epilepticus. Blood glucose measurement should be obtained when patients are symptomatic. Treatment includes intravenous administration of 1 or 2 ampules of glucose (50 g/ampule) and this should be supplemented with thiamine.

NEUROLOGIC CONDITIONS ASSOCIATED WITH SYSTEMIC VASCULITIS

Systemic Lupus Erythematosus (SLE)

SLE is immune-mediated multisystem inflammatory disorder, diagnosed by the presence of autoantibodies directed against varied components of the cell nucleus e.g. antinuclear antibodies. Joint and dermatological manifestations are most common; pulmonary, cardiological, and renal manifestations may occur. CNS involvement usually occurs late in course of SLE, although rarely it can be the initial symptom. It usually involves central (brain, spinal cord) but may involve peripheral nervous system. Pathologic features include multiple small infarctions caused by arteriolar and capillary occlusions, large vessel nonvasculitic infarctions, and rare instances of multifocal necrotizing angitis with fibrinoid degeneration. It

should be noted that despite “vasculitis” being seen pathologically, the exact mechanism of neuropsychiatric manifestations of SLE are not known and can be multiple, including nonbacterial thrombotic endocarditis and valvular inflammatory disorder, which causes cardiogenic cerebral embolism, thrombotic thrombocytopenic purpura, infectious-inflammatory disorders or thrombotic coagulation states. Neurologic findings of SLE are listed in Box 22-3. Less commonly, patients with SLE have clinical evidence of peripheral nervous system involvement including polyneuropathy, mononeuritis multiplex, or myopathy. Contrasted with CNS pathologic findings peripheral nervous system is affected by systemic vasculitis as demonstrated by nerve or muscle biopsy findings. CSF findings in lupus cerebritis can include pleocytosis, elevated protein content with increased gamma-globulin component, and decreased complement level. Most patients with neurologic abnormalities have evidence of renal impairment and decreased serum complement level. Consistent with pathologic findings, angiography usually shows no evidence of vasculitis.

Improvement of neurologic function in SLE usually follows treatment with corticosteroids (prednisone, 60-120 mg/day), but ultimate prognosis is determined by severity of systemic manifestations e.g. renal. In patients who have suffered SLE related stroke and have marantic nonbacterial endocarditis or antiphospholipid antibody syndrome, anticoagulation should be considered. In SLE patients receiving corticosteroids, the onset of neuropsychiatric symptomatology suggests several diagnostic possibilities: lupus cerebritis, corticosteroid-induced psychoses, single or multiple stroke episodes, infectious-inflammatory disorders caused by immunologic abnormalities secondary to SLE or immunosuppressive medication effect.

Periarteritis Nodosa (PN)

PN is a systemic necrotizing inflammatory arteritis that affects medium and small vessels. Arteritis predisposes patients to thrombosis with ischemia and infarction; aneurysms can develop in involved vessels. Patients with PN have gastrointestinal, renal, or cardiac symptoms; neural involvement occurs in 50%. CNS manifestations include stroke syndromes as a result of thromboembolism or intracranial hemorrhage caused by ruptured inflammatory aneurysms. Peripheral nervous system involvement consists of mononeuritis multiplex, polyneuropathy, or myopathy. The diagnosis of PN is established by nerve or muscle biopsy, showing pathologic evidence of vasculitis. Corticosteroids combined with cyclophosphamide have been efficacious in PN.

Antiphospholipid Antibody Syndrome (APL)

These include lupus anticoagulant (LA) and anticardiolipin (ACL) antibodies. They represent polyclonal immunoglobulins that bind negatively charged phospholipids. They can cause recurrent thrombotic events in both arterial and venous circulations. These patients can have ischemic stroke syndrome, retinal artery occlusion, seizures, chorea, multiinfarct dementia or migraine. These patients often have a history of prior deep vein thrombosis, multiple spontaneous abortions, and skin lesions classified as livedo reticularis. A stroke in young person should initiate investigation for APL syndrome. Laboratory findings can include false positive VDRL (syphilis) serology, low platelet count, prolonged prothrombin and activated partial thromboplastin time, positive antinuclear antibody, and LA and ACL antibodies.

Echocardiogram can show thrombotic vegetations on heart valves. Cerebral angiogram shows single or multiple intracranial arterial occlusions without evidence of vasculitis. Treatment is controversial and includes suppression of immune mediated thrombotic response using steroids or immunosuppressive medication (azathioprine, methotrexate, cyclophosphamide); plasmapheresis to reduce thrombotic-producing antibodies; and reducing arterial thrombotic state with anticoagulant or antiplatelet medication.

Rheumatoid Arthritis

This is immune complex mediated disorder involving the synovial membrane. Characteristic clinical features include morning stiffness, symmetric polyarthritis (metacarpophalangeal, proximal interphalangeal, wrist, elbow, knee, ankle and cervical spine). Rheumatoid nodules are found in subcutaneous tissue. Predominant neurological disorders are due to cervical spine atlantoaxial subluxation involving C-1 and C-2. Compression of the upper cervical spine may develop causing cervical myelopathy. Peripheral nerve disease is common in rheumatoid arthritis patients. Median and ulnar nerve entrapment are common at the wrist, due to rheumatoid changes.

HEMATOLOGIC DISORDERS

Vitamin B₁₂ Deficiency (Subacute Combined System Disease)

Pernicious anemia is the most common cause of B₁₂ deficiency; other causes include gastrointestinal disorders (blind loop syndromes, tapeworm, celiac disease, vegetarian diet). B₁₂ deficiency can develop in dentists and anesthesia personnel who abuse nitrous oxide; this inactivates B₁₂. Most patients are usually anemic (macrocytic) with megaloblastic bone marrow. They have low serum B₁₂ level and decreased hydrochloric acid secretion. Neurologic symptoms can develop in patients who are not anemic but who have low B₁₂ levels (<200 pg per ml). Definitive diagnosis is established by serum determination of methylmalonic acid and homocysteine levels; these accumulate when B₁₂ – dependent reactions are blocked. Pernicious anemia is believed to be immune-mediated because antibodies to gastric parietal cells and intrinsic factor are commonly identified and other immune-mediated conditions occur in association with pernicious anemia.

The earliest pathologic change is myelin sheath swelling. This involves large diameter fibers; later myelin is destroyed and axon is affected. Sensory disturbances are initial neurologic manifestation. Clinical findings are sensory ataxia, impaired position and vibration sense, areflexia, and bilateral Babinski signs. Onset is subacute; peripheral neuropathy, not myelopathy, represents the initial findings of neurological B₁₂ deficiency. Neurological findings include myelopathy, peripheral neuropathy, and neuropsychiatric disorders (i.e., irritability, hallucination, confusion, dementia). Despite pathologic findings of diffuse CNS demyelination, relationship of mental aberrations to B₁₂ deficiency is not clear. Treatment consists of intramuscular B₁₂ injection. The prognosis is best in patients who have a short duration of symptoms. In patient with folate and B₁₂ deficiency, it is a long-believed but inconclusively proved myth that treatment with folate only can precipitate neurologic symptoms of B₁₂

deficiency. Cyanocobalamin or hydroxocobalamin can be administered intramuscularly or subcutaneously; however, oral preparations are not effective.

Hemolytic Anemias

Disorders characterized by shortened red blood cell survival time can be broadly classified into two groups: intrinsic defect in red cell composition including hemoglobinopathies (sickle cell disease) and extrinsic abnormal factors in plasma (autoimmune disorders).

Hemoglobinopathies

Inherited disorders of hemoglobin synthesis that cause abnormal neurologic features include hemoglobin SS and SC disease. Neurologic disorders are rare in patients with the sickle cell trait (hemoglobin SA). The pathophysiologic mechanism of cerebrovascular complications is vascular occlusion caused by sickling. This causes increased blood viscosity, endothelial capillary damage, and activation of coagulation mechanism to cause thrombosis. Precipitating factors for sickling include hypoxia, dehydration, and metabolic acidosis. These can cause the formation of deoxyhemoglobin. This causes Hgb S molecule to become insoluble and polymerize to deform red blood cell. If patient is dehydrated, this increases Hgb S concentration as result of reduced water content, and blood has increased viscosity, which results in vascular thrombosis. This is initially seen in small vessels and later in larger vessels. Vascular thrombosis leads to cellular hypoxia, which increases vascular sickling. There can be involvement of large and small intracranial vessels. This especially involves border zone between major arteries such as middle and posterior cerebral arteries. Spinal cord infarction can be caused by sickle cell disease. This diagnosis should be suspected in young black patients who develop paraparesis. Diagnosis of sickle cell (SS) disease is established by blood smear (showing sickling) and hemoglobin electrophoresis. Common neurologic manifestations include ischemic stroke syndromes in younger patients and hemorrhagic stroke in adults. As sickle cell disease progresses there is progressive narrowing of large intracranial vessels. This can be detected with transcranial Doppler studies or angiography; vascular occlusions are frequently recurrent leading to recurrent clinical strokes. Visual disturbances result from retinal circulation occlusive disease. The diagnosis of cerebral infarction can be established by CT/MRI scan; transcranial Doppler is best simple noninvasive technique to detect intracranial vascular change – this can also be followed with MRA. Angiography demonstrates site of vascular occlusion; it should be performed with caution because iodinated contrast can precipitate sickling. Treatment of sickle cell patients with acute stroke includes hydration, correction of metabolic abnormalities including acidosis (use bicarbonate), oxygen administration, and treatment of the identified intercurrent infection. Treatment of patients with sickle cell disease is repeated exchange transfusions to maintain Hgb SS at less than 30%. Bone marrow transplantation may play role to prevent stroke in certain patients with severe vascular disease.

Polycythemia Vera

Neurologic disorders in polycythemia vera are caused by occlusive thrombotic (hyperviscosity, platelet clumping, thrombocytosis) and hemorrhagic (abnormal thromboplastin

formation) stroke. Other clinical disturbances include headache, lethargy, dizziness, vertigo, and papilledema. Polycythemia occurs in association with cerebellar hemangioblastoma, hepatic and renal disease, uterine fibroids, and hypoxia. Treatment of neurologic symptomatology resulting from hyperviscosity includes phlebotomy.

Hemorrhagic Disorders

Hemorrhagic disorders occur in congenital (e.g., hemophilia) or acquired disorders (e.g., hepatic disease, leukemia, anticoagulant therapy). In hemophilia, bleeding can cause peripheral (nerve or plexus) or intracranial (subdural, subarachnoid, intracerebral) lesions. Peripheral nerve compression lesions are the most common neurologic complication of hemophilia; these are usually secondary to intramuscular bleeding (spontaneous or traumatic). In hemophilia patients, sudden development of neurologic abnormalities is evidence of recent bleeding; blood replacement therapy is initiated, and surgery is usually avoided. In anticoagulated patients the effects of heparin can be reversed rapidly by intravenous protamine (2 mg/ml). The effects of warfarin are reversed rapidly by infusing fresh frozen plasma or more slowly (within 6-12 hours) with intravenous vitamin K (50 mg). Intracranial hemorrhage can also occur in patients treated with thrombolytic agents (urokinase, streptokinase, tissue plasminogen activator).

Thrombotic Thrombocytopenic Purpura (TTP)

The diagnosis of TTP is established by these criteria:

- Neurologic disturbances
- Thrombocytopenia
- Hemolytic anemia
- Fever
- Renal impairment

Neurologic manifestations include altered consciousness, focal neurologic deficit, seizures, retinal hemorrhages, papilledema. Pathologic findings include platelet-rich thrombi and endothelial hyperplasia; these thrombi are associated with necrotic and petechial hemorrhagic lesions. Most patients die within several weeks. Treatment with heparin, corticosteroids, plasma exchange, or plasma infusion have been unsuccessful; however, remission following exchange plasmapheresis and antiplatelet agents (aspirin and dipyridamole) can occur.

Disseminated Intravascular Coagulopathy

Diffuse intracranial thrombotic lesions are caused by activation of a coagulation mechanism with fibrin deposition on the endothelial wall with fibrinolytic response. Pathologic findings are fibrin thrombi in small intracranial vessels. These can result in infarction or multifocal hemorrhages. Hemorrhagic lesions result from consumption of coagulation factors and platelets in addition to the coagulant effect of fibrin-split products. Conditions causing tissue damage such as surgery, sepsis, or trauma can result in the release of tissue thromboplastin and coagulation system activation. Neurologic manifestations depend on number, distribution,

and type of lesions(s). Multifocal microvascular thrombotic lesions cause encephalopathy, and large intracerebral hematoma cause altered consciousness and focal neurologic deficit.

Oral Contraceptive Pills (OCP)

Neurologic complications of OCP are due to hypercoagulability (effect on platelets, protein S, protein C, antithrombin III factor). These effects can be correlated with OCP estrogen content. There is increased risk of thromboembolic phenomena in patients who have used OCP containing estrogen with excess of 50 µg per tablet, and laboratory studies can demonstrate hypercoagulability. Neurologic complications include cerebral arterial thromboembolism, venous sinus thrombosis, benign intracranial hypertension, retinal vascular disease, and migraine. The incidence of stroke syndrome in young women has increased in the four decades since introduction of OCP; however, it is important to know that pregnancy is also associated with the increased risk of stroke. Migraine is sometimes exacerbated in both frequency and intensity by these drugs, but it is not known if the development of migraine increases stroke risk. Those patients who use OCP, smoke cigarettes, are hypertensive or have family history of hypertension, and are older than 35 years old have the highest stroke risk.

ANOXIC-ISCHEMIC BRAIN DISORDERS

Subacute and Chronic Hypoxic Encephalopathy

Subacute and chronic hypoxic encephalopathy occurs in patients who have inadequate brain oxygen content as a result of certain disorders including pulmonary dysfunction, anemia, and low cardiac output (congestive heart failure and aortic stenosis). Neurologic symptomatology can develop if oxygen content is less than 55 mmHg. Neurologic manifestations include irritability, agitation, impaired judgment, confusion, and myoclonus. This condition can persist for several weeks to months if the underlying cause is not corrected; however, if another acute event (rapid decrease in cerebral blood flow and perfusion, febrile illness, anesthesia) is superimposed, acute anoxic-ischemic brain damage can worsen neurologic function.

Acute Anoxic-Ischemic Encephalopathy

In patients who require cardiopulmonary resuscitation inadequate support of brain function can cause neurologic sequelae. If cerebral circulation is terminated for more than 10 seconds, brain oxygen reserves are depleted, and neurologic dysfunction (i.e., lightheadedness, blindness, altered consciousness, myoclonus, decerebration, pupillary dilatation, Babinski signs) can develop. After successful resuscitation from any shock state, (e.g., sepsis, smoke inhalation, carbon monoxide poisoning, strangulation, cardiac arrest) complete recovery can occur or patient can develop mild amnestic syndrome.

In certain cases a hypoxic episode causes cerebral edema and ischemia. Postanoxic ischemia is most commonly encountered after cardiac arrest in which there has been cessation of cerebral blood flow. Cerebral ischemia can be diffuse (global) or focal. In these cases ischemic

changes occur in border zone regions (territory between anterior and middle cerebral arteries or between posterior and middle cerebral arteries). Swelling of capillaries is postulated to decrease blood flow, and this can persist even if cerebral circulation is adequately restored. Decreased tissue perfusion can cause permanent neurologic deficit including amnesia, dementia, blindness, weakness (bibrachial paresis, quadriparesis), myoclonus, ataxia, seizures, or extrapyramidal (parkinsonism, hemiballism) disorders. In certain cases of hypoxic-ischemic injury there is severe neocortical brain damage with intact brain stem and spinal cord reflexes. These patients are severely neurologically impaired but can survive for prolonged periods in vegetative states. In cases of irreversible coma (brain death) cortical function and brain stem reflexes are absent. Anoxia affects the myocardium and brain; therefore there is also myocardial ischemia with anoxic brain damage. This is manifested by electrocardiographic changes and elevated serum enzymes (creatine phosphokinase, CPK). Because a portion of CPK originates from brain, isoenzyme patterns can be required to determine the exact enzyme source (e.g., skeletal or myocardial muscle, brain). Following initial stabilization or recovery from anoxic injury, certain patients subsequently deteriorate one to three weeks later. Findings include altered consciousness, rigidity, spasticity, and Babinski signs. Pathologic findings are diffuse demyelination involving cerebral white matter; however, the cause of delayed postanoxic encephalopathy is unknown.

Pulmonary Encephalopathy

In patients with carbon dioxide retention and respiratory acidosis caused by acute respiratory disorders, neurologic symptomatology (altered mentation, generalized seizures, myoclonus, asterixis) can develop. Headache that occurs at night or immediately upon awakening is due to nocturnal hypoventilation and CO₂ retention. Other conditions such as emphysema, bronchitis, and massive obesity (pickwickian syndrome) cause chronic hypercapnia. Neurologic dysfunction can develop as a result of elevated arterial carbon dioxide levels, decreased arterial oxygen levels, or decreased arterial bicarbonate levels (respiratory acidosis); these disturbances result in cerebral vasodilation. Neurologic manifestations include intracranial hypertension; encephalopathy with altered consciousness, asterixis, or myoclonus; and diffuse EEG slowing. Narcosis developing in patients with chronic hypercapnia is quite different from an agitated confusional state caused by hypoxia. Treatment of carbon dioxide retention should initially include assisted ventilatory support because the brain stem respiratory centers are depressed and treatment with oxygen alone may not be effective. Sleep apnea syndromes are associated with cardiovascular and respiratory disturbances. Hyperventilation can occur in anxiety states and can cause paresthesias involving extremities or the perioral region, light-headaches, muscle cramps, capopedal spasms, and occasionally brief periods of unconsciousness.

SARCOIDOSIS

Sarcoidosis is a systemic granulomatous disorder of unknown cause. It can involve the nervous system and in some patients, neurologic manifestations are the initial signs. Pathologic CNS findings are basilar meningitis with thickening of meninges and diffuse noncaseating granulomatous nodules; rarely granulomas extend into the brain parenchyma and spinal cord.

Sarcoid granulomas can be seen peripherally (nerve, muscle). Neurologic manifestations in sarcoidosis, except when caused by hypercalcemia, are secondary to granulomas and basilar meningitis. Neurologic features for sarcoidosis are listed in Box 22-4. In sarcoid meningitis, CSF findings include sterile pleocytosis with lymphocyte predominance, decreased sugar content, elevated protein content, and negative studies for infectious causes. CT/MRI may show meningeal enhancement with evidence of nodular lesions located along basal cisternal and dural convexity regions as well as showing hydrocephalus. To establish the diagnosis of sarcoidosis, biopsy evidence is necessary (lymph nodes, liver, skin, conjunctiva, muscle), but confirmation of CNS involvement can require dural or brain biopsy. Some patients with neurosarcoid have a monophasic course; others have chronic remitting-relapsing course.

Treatment of neurologic symptoms with corticosteroids (prednisone, 60-120 mg/day) is usually efficacious, but this must be continued for several months to years. If lesions do not respond to prednisone, consider high-dose intravenous methylprednisone. For refractory cases of neurosarcoidosis, radiation therapy or immunosuppressive medication can be used. Spontaneous remission and recurrence can characterize the course of neurosarcoidosis. Hydrocephalus can require a shunting procedure, and hormonal replacement may be needed if there is hypothalamic-pituitary dysfunction. Intracranial granulomas rarely require surgical removal, if they compress neural structures and do not respond to corticosteroids.

PORPHYRIA

Several disorders of porphyrin metabolism are associated with neurologic symptomatology including acute intermittent porphyria (AIP), hereditary coproporphyria, and variegate porphyria. AIP is inherited as an autosomal dominant trait and is characterized by increased production of delta-aminolevulinic acid and porphobilinogen (PBG) due to deficiency of porphobilinogen deaminase. These are porphyrin precursors and are excreted in urine. Urine contains increased amounts of coproporphyrin and uroporphyrin. AIP is believed to result from uroporphyrin synthetase deficiency. Pathologic findings include neuronal degeneration with central and peripheral white matter demyelination. Patients have abdominal crisis; these features are believed caused by autonomic dysfunction. Other symptoms are due to central (mental changes with confusion, delirium, psychoses with hallucinations, mania or depression, seizures, hyponatremia, water intoxication) or peripheral (acute or subacute ascending paralysis) nervous system involvement. In rare instances symptoms and signs caused by brainstem dysfunction including dysarthria, dysphagia, diplopa, ophthalmoplegia, respiratory depression, and hypertensive vascular crisis develop.

Acute attacks of AIP can be precipitated by drugs (barbiturates, sulfonamides, oral contraceptives, estrogen, alcohol), fasting state, or hormonal shifts (menstruation). It is possible that these induce delta-aminolevulinic acid dehydrase and that during attacks this enzyme can be hyperactive. During acute attacks, urine appears burgundy red and darkens in the test tube; it contains no red blood cells and gives a negative hemoglobin reaction. The Watson-Schwartz test for PBG is usually positive during attacks, but negative test does not exclude AIP. During acute episodes avoidance of exacerbating drugs, monitoring of respiratory function, careful fluid replacement, opiates to control pain, and phenothiazines for psychoses are effective treatment. Many anti-epileptic medications may exacerbate AIP. Gabapentin is effective and safe. During

an acute attack of porphyria treat seizures with intravenous 10% glucose and hematin; both act to lower hepatic delta-aminolevulinic acid synthetase activity. The role of chelating agents in AIP is controversial. Fluid management is necessary as SIADH can occur to cause hyponatremia. Pain should be managed carefully using low dose phenothiazines or meperidine only if absolutely necessary.

NEUROLOGIC COMPLICATIONS OF PREGNANCY

Cerebrovascular Disease

The incidence of stroke in pregnant women is higher than in nonpregnant women including those using oral contraceptives. Potential mechanisms of stroke in pregnancy include disseminated intravascular coagulation caused by abruptio placentae, venous sinus and cortical vein thrombosis; and hemorrhage caused by metastatic choriocarcinoma, eclampsia, and ischemic arterial cerebrovascular disease. Estrogen causes hypercoagulability, increased platelet aggregation; hypertension alters lipid levels and affects arterial wall integrity. These effects may lead to arterial and venous infarcts and berry aneurysm rupture. Reversible segmental arterial vasoconstriction (vasospasm) may cause arterial stroke during pregnancy. Peripartum cardiomyopathy and paradoxical embolus from pelvic vein in the patient with patent foramen ovale may cause cardiogenic cerebral embolus. Anticoagulation with warfarin is avoided and subcutaneous heparin is used during pregnancy.

Eclampsia

Eclampsia is hypertensive disease that occurs in pregnant women and terminates soon after childbirth. There is breakdown in cerebral autoregulation. Neurologic manifestations include headache, visual symptoms (blurring, visual field defect, cortical blindness), hyperreflexia, Babinski signs, seizures, and altered consciousness. If focal deficit occurs, this suggests intracerebral hemorrhage or infarction. In eclampsia pathologic findings include brain swelling with edema, small infarctions, hemorrhage, and vasospasm. There is a predilection for pathologic changes in the parieto-occipital cortex. Management of eclampsia includes rapid lowering of blood pressure and pregnancy termination. Seizures usually stop with blood pressure control; however, anticonvulsants (diazepam, lorazepam, phenytoin) may be needed. Magnesium sulfate can be used as anticonvulsant for eclampsia and is the preferred agent! This drug blocks autonomic and neuromuscular transmission; therefore it can cause respiratory depression and arrhythmias and must be used with caution.

Seizure

For a discussion of those seizures not caused by eclampsia, see chapter 11.

Headache

Migraine usually improves during pregnancy. If migraine does occur, ergots should be

avoided because they may stimulate uterine contractions. Treatment of migraine during pregnancy should focus on the following: avoid precipitating factors, utilize acetaminophen rather than aspirin, triptan use appears effective and safe. Treat vomiting with intravenous fluids and anti-emetic medication. New onset of headaches in pregnant women must be assessed carefully neurologically. The need for diagnostic studies is determined by the presence of abnormal neurologic findings. Brain neoplasms and vascular malformations can expand in size as a result of increased tumor vascularity, and symptoms can progress during later pregnancy stages.

Multiple Sclerosis

There is little evidence to support the belief that pregnancy exacerbates multiple sclerosis. It is important for patients with multiple sclerosis to avoid fatigue in the postpartum period when MS exacerbates.

Neuromuscular Disease

Mononeuropathies (e.g., facial paralysis, median nerve compression at carpal tunnel, lateral femoral cutaneous nerve involvement) are common in pregnancy. Nutritional neuropathy and Wernicke-Korsakoff syndrome can occur in patients with hyperemesis gravidarum. Lumbosacral joint laxity and the weight of the fetus in the abdomen can cause mechanical back strain symptoms. Obstetrical complications include peroneal, femoral, and sciatic neuropathy. Transient myasthenia gravis occurs in newborns of myasthenic mothers (See Chapter 7).

SUBSTANCE ABUSE

Narcotics

Narcotics include morphine, heroin, hydromorphone (Dilaudid), oxycodone (Percodan Oxycontin), methadone, fentanyl (Sublimaze, Duragesic). Major neurologic complications are due to overdoses and include coma, respiratory depression, miotic pupils, and death. Treatment includes respiratory and cardiac support. Naloxone is administered in doses of 0.4 mg every 5 minutes to reverse narcotic effects. Naloxone has short half-life as contrasted to longer half-life of certain drugs of abuse and the naloxone dose may need to be repeated. If patient does not respond, use flumazenil (0.2 mgm per minute to maximum of 3.0 mgm per hour) to determine if coma is due to benzodiazepine. If recovery from an acute overdose occurs, neurologic sequelae can develop. These include seizures, dementia, delayed postanoxic encephalopathy, stroke, and dyskinesias. Toxic optic neuropathy can result from quinine, used as a diluent for "street-made" illicit narcotics. Transverse myelitis can occur in patients who use intravenous heroin once again after there has been a period of abstinence, for example, after release from prison. Compressive neuropathies can result from injection into a nerve or from tourniquet-induced nerve ischemia. After a prolonged narcotic coma, myoglobinuria can result. Infections occurring commonly in narcotic addicts include tetanus, local abscesses, osteomyelitis, endocarditis, and hepatitis. Withdrawal symptoms include marked signs of sympathetic over discharge and agitated delirious

state.

Stimulants

Cocaine and amphetamine (Dexedrine, methylphenidate [Ritalin] phenylpropalamine [PPA], methamphetamine, methylenedioxymethamphetamine [Ecstasy]) are commonly used stimulant drugs. Cocaine causes heightened awareness and perception, agitation and anxiety, and an increased sympathomimetic discharge (tachycardia, hypertension). Seizures and cardiac arrest (because of arrhythmias) can also result. An acute hypertensive crisis severe enough to cause intracranial hemorrhage can result from the reuptake block of sympathomimetic neurotransmitters induced by cocaine. Amphetamines can produce an acute agitated delirious state, paranoia, hallucinations, and seizures. Following the use of methamphetamine, cerebral vasculitis can cause stroke. Methylphenidate hydrochloride (Ritalin) can be mixed with certain substances (starch) and injected intravenously. The particulate matter can embolize to the brain to cause stroke by damaging blood vessel and causing vasospasm.

Hallucinogens

Hallucinogens include lysergic acid diethylamide (LSD), phencyclidine (PCP), and mescaline. LSD causes prominent behavioral manifestations (psychoses, acute anxiety, panic states, hallucinations). PCP causes psychoses, autonomic over discharge (with cardiovascular effect and dilated pupils), and seizures. Fatal status epilepticus has been reported with PCP use.

Pentazocine and Pyribenzamine

Pentazocine (Talwin) and an antihistamine Pyribenzamine tablet are usually crushed and mixed with water (T's and blues) and injected intravenously. They can produce embolic particles, which cause stroke.

GASTROINTESTINAL DISORDERS

Pancreatic Disease

It is believed that some patients with chronic pancreatitis develop "pancreatic encephalopathy." This disorder is characterized by an agitated confusional state with hallucinations, speech disturbances, muscular rigidity, and quadriplegia. Pathologic findings include petechial hemorrhages and demyelination seen in subcortical and brain stem regions. It is important to consider pancreatic disorders in adult patients with otherwise unexplained neurobehavioral symptoms of recent onset. Pancreas tumors (insulinomas) can cause intermittent hypoglycemia with perplexing array of neurobehavioral manifestations.

Celiac Disease

Celiac disease is an idiopathic steatorrhea with malabsorption caused by small intestinal disease. The condition remits when a gluten-free diet is instituted. Neurologic features occur in 10% of patients and include myopathy, neuropathy, cerebellar ataxia, myoclonus, seizures, encephalopathy. Myopathy is associated with osteomalacia as a result of abnormal calcium and vitamin D metabolism. Neuropathy and ataxia can be due to vitamin E deficiency. Seizures can be due to calcium, magnesium, or pyridoxide deficiency.

WHIPPLE DISEASE (See Infectious Disease, Chapter 18)

NEUROLOGIC COMPLICATIONS OF ORGAN TRANSPLANTATION

These can include the neurologic effect of underlying condition for which organ transplantation was performed, for example, diabetes, hypertension, and SLE; immunosuppressive therapy can cause nervous system toxicity and impair immunologic response to result in opportunistic infections, for example, *Cryptococcus* and *Listeria monocytogenes* or neoplasms, such as lymphomas, as well as the direct effect of the specific organ transplantation.

In patients undergoing renal transplant cerebrovascular disorders (ischemic, hemorrhage) are the most common complication. Following cardiac transplantation, perioperative hypoxic-ischemic complications are most common. Other complications of heart transplants include cardiogenic cerebral embolism, opportunistic infections, lymphoma. Of patients undergoing liver transplant, neurologic complications including encephalopathy, seizures, and focal neurologic deficit are common. Intracranial hemorrhage and opportunistic infection are common causes of these liver transplant complications. In patients undergoing bone marrow transplants (BMT) an immunological reaction of donor T lymphocytes against recipient tissues (graft versus host reaction) occurs. Acute phase causes no neurological symptoms but chronic manifestations include polymyositis, myasthenia gravis, neuropathy, aseptic meningitis and leukoencephalopathy. Neurological manifestations of BMT are brain hemorrhage, encephalopathy and CNS infections.

The outcome of transplants is highly dependent upon the prevention of host rejection. This must be prevented by suppressing the recipient immune system. The following drugs have neurotoxicity: cyclosporine, methotrexate, cytarabine, corticosteroids, OKT-3, monoclonal antibody. Cyclosporine has hepatic, renal, and neurologic toxicity. It is lipophilic and can cause adverse CNS effects, including encephalopathy, seizures, tremor, ataxia, leukoencephalopathy, and burning extremity dysesthesias. Cyclosporine-induced leukoencephalopathy – characterized by confusional state, ataxia, cortical blindness, motor deficit (paraparesis, quadriparesis) – may simulate clinical features of progressive multifocal leukoencephalopathy. Sustention and intention tremor is the most common neurologic adverse effect of cyclosporine. Much of cyclosporine toxicity is related to hypertensive effect and impaired cerebrovascular impaired autoregulation and associated magnesium deficiency. MRI shows hyper-intensity in parietal-occipital white matter. Tacrolimus (Prograf) is less neurotoxic than cyclosporine but pattern of effect is similar. Methotrexate can cause neurotoxic syndrome consisting of aseptic meningitis or transverse myelitis, especially if administered intrathecally. Stroke-like syndromes and

leukoencephalopathy have also been reported (especially when combined with cranial irradiation). Monoclonal antibody OKT-3 can cause fever, chills, shaking spells, tremor, and headache as well as aseptic meningitis. Cytarabine can cause peripheral neuropathy and myelopathy. Corticosteroids effects are described elsewhere.

NEUROLOGIC ADVERSE EFFECTS OF NEOPLASTIC THERAPY

They can have central or peripheral nervous system toxicity (Box 22-5). They may cause peripheral neuropathy as well as cranial and autonomic neuropathy. CNS symptoms include encephalopathy, cerebellar syndrome and spine myelopathy. They may have more serious toxicity when combined with radiotherapy.

NEUROLOGIC EFFECTS OF CARDIAC SURGERY

Neurologic sequelae are stroke, hypoxic-ischemic encephalopathy, and diffuse encephalopathy as results of multiple surgical, medical, and anesthetic factors. With extracorporeal circulation there are coagulation factor abnormalities and blood pressure fluctuations that can result in microembolization. Following surgery patients may report memory, cognitive, and behavioral abnormalities. With improved extracorporeal systems that use microfilters, neuropsychologic sequela is less common now than in the past. Ischemic (carotid and vertebral-basilar) thromboembolic and cardiogenic cerebral embolic stroke can result from cardiac surgery, and intracranial hemorrhage can result from anticoagulant and thrombolytic medication. Focal neuropathies or brachial plexus dysfunction can complicate cardiac surgery because of stretch injuries secondary to patient positioning. In patients undergoing cardiac transplantation, immuno-suppression is common cause of neurologic complications, for example, aspergillosis, toxoplasmosis.

CHRONIC FATIGUE SYNDROME (CFS)

Fatigue is a state of discomfort and decreased mental and motor efficiency resulting from excessive exertion. This is relieved by rest and avoided by conditioning efforts. Chronic persistent fatigue that develops without the exertion necessary to cause exhaustion in normal people represents as perplexing and poorly defined disorder. In one study 21% of patients who came to primary care physicians had chronic fatigue as their chief complaint. The definition of CFS includes persistent and recurrent fatigue lasting at least 6 months, fatigue not improving with bed rest, activities of daily living reduced by 50%, and other medical, neurologic, rheumatologic, infectious, and psychiatric illnesses causing fatigue have been excluded. Other symptoms of CFS include low-grade fever, pharyngitis, lymphadenopathy, myalgia, postexertional malaise, arthralgia, memory and cognitive disturbances, headache, and sleep disturbances. CFS frequently follows viral infections such as infectious mononucleosis, and an antigen of Epstein-Barr virus can be demonstrated by serological studies.

Fatigue symptoms can be a prominent feature of multiple sclerosis, parkinsonism,

myasthenia gravis, postpolio syndrome, and postconcussion syndrome, and these disorders should be excluded by careful neurologic examination before establishing the diagnosis of CFS. Fatigue can be seen in psychiatric disorders including affective and somatization disorders however, psychogenic fatigue is characterized by fatigue present upon awakening in morning and is constantly present throughout day. In CSF neurodiagnostic studies show no abnormalities; however, certain inconsistent immunologic abnormalities have been reported (lymphocytosis, hypo- or hypergamma-globulinemia, antinuclear antibodies, serologic evidence of Epstein-Barr virus infection). It is believed that multiple triggering events (infection, trauma, physical or emotional stress) can trigger immunologic response with elaboration of cytokines and trigger CFS. Symptomatic treatment using amantadine, stimulants, and antidepressants have variable success. Many patients who develop CFS after clearcut viral illness recover slowly; however, other patients with CFS remain permanently disabled.

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Box 22-1. Neurologic Complications of Alcohol

Acute intoxication

Euphoria
Impaired judgment and coordination deficit
Decreased inhibition
Memory lapses (blackouts)
Nystagmus, ataxia, dysarthria, diplopia
Pathologic intoxication (acute agitated excited state with violent behavior)
Acute auditory hallucinosis
Stupor and coma
Hypothermia, hypotension, hypoventilation
Death caused by respiratory or cardiovascular collapse

Withdrawal syndrome

Tremulousness
Seizures
Hallucinosis
Delirium tremens

Nutritional-related alcoholic

Wernicke-Korsakoff syndrome
Toxic amblyopia (optic neuropathy)
Peripheral neuropathy

Disorder of unknown pathogenesis

Cerebellar degeneration
Myopathy
Dementia and cerebral atrophy
Marchiafava-Bignami disease
Central pontine myelinolysis

Disorders related to hepatic failure

Asterixis
Non-Wilsonian hepatolenticular degeneration
Coma
Spastic paraparesis
Subdural and intracerebral hematoma related to coagulopathy

Box 22-2

1. Adequate fluid replacement to prevent dehydration resulting from fever, intense motor activity, and inadequate fluid intake except for alcohol
 2. Parenteral glucose and multivitamins including high-dose thiamine
 3. Sedative medication (chlordiazepoxide, lorazepam) and avoidance of drugs impairing cardiac function (diazepam or chlorpromazine)
 4. Investigation for systemic infection, hepatic or hematologic dysfunction, and intracranial (traumatic or infectious) lesions
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Box 22-3

1. "Lupus cerebritis with symptoms including confusion, dementia, psychoses, seizures, cortical blindness
 2. Stroke syndromes including subarachnoid and parenchymal hemorrhage or ischemic stroke due to thrombotic intracranial due to hypercoagulability lacunar infarcts due to hypertension, cardiogenic cerebral embolism due to marantic endocarditis
 3. Migrainelike headaches, which occur in more than 50% of SLE patients and respond to conventional migraine treatment
 4. Papilledema
 5. Myelopathy
 6. Dyskinesias, especially chorea
Cranial neuropathies involving facial, oculomotor, trigeminal, acoustic nerves
-

Box 22-4

1. Cranial nerve palsies of which facial nerve involvement is most frequent, but papillary abnormalities are usually secondary to uveitis, not oculomotor involvement
 2. Chronic or subacute meningoencephalitis
 3. Mass effect caused by intracranial granuloma
 4. Symptoms of hydrocephalus caused by obstruction of fourth ventricle or basal cisterns
 5. Juxtaseellar syndrome (visual defects, diabetes insipidus, hypopituitarism) caused by hypothalamic-pituitary granuloma
 6. Seizures caused by cortical granulomas or vasculopathy
 7. Peripheral neuropathy, mononeuritis multiplex
-

Box 22-5

1. *Methotrexate*. When this drug is administered intrathecally, acute neurotoxicity includes aseptic meningitis and transverse myelopathy. Following high-dose intravenous methotrexate, stroke-like syndrome and leukoencephalopathy (which may be delayed or chronic effect) can develop, especially when methotrexate is combined with cranial irradiation.
 2. *Cisplatin* is antineoplastic drug that has a heavy metal base; therefore, it is not surprising that it can cause peripheral neuropathy. Neuropathy involves large sensory fibers, and findings are absent deep tendon reflexes, reduced vibration and position sensation, and sensory ataxia. Cisplatin can also cause ototoxicity and vestibular dysfunction. Carboplatin has similar antineoplastic effects but minimal neurotoxicity.
 3. *Vincristine* and *vinblastin* are vinca alkaloids and frequently cause peripheral or cranial neuropathy. It is rare for the vincristine-treated leukemic patient to have intact ankle jerks and normal vibration sensation in the feet.
 4. *Asparaginase*. This interferes with coagulation mechanism (interfering with anti-thrombin III) to cause venous thrombosis (see chapter ??).
 5. *Procarbazine* can act as a monoamine oxidase inhibitor and cause encephalopathy or manic psychotic episodes. Patients must be advised to avoid tyramine-containing food or sympathomimetic medications.
 6. *5-fluorouracil* can cause cerebellar disorders such as ataxia, dysmetria, and tremor.
 7. *Cytosine arabinoside* can cause aseptic meningitis or transverse myelopathy if administered intrathecally or cerebellar syndrome if administered intravenously.
 8. *Taxol* is a naturally occurring antineoplastic agent that causes peripheral neuropathy.
 9. *Tamoxifen* is a hormonal agent (synthetic anti-estrogen) used in breast cancer treatment that can cause encephalopathy, cerebellar syndrome, retinopathy, or optic neuropathy.
 10. *Doxorubicin*. After parenteral use, it may cause cardiac thrombus, which results in stroke syndrome.
 11. *Suramin*. This may cause demyelinating (rapidly progressing) motor neuropathy that is reversible after
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Box 22-5

drug is discontinued.

12. *Cranial irradiation* can cause acute, early delayed (1 or 3 months later) or late delayed (after 3 months) syndrome. Acute encephalopathy most commonly develops in patients treated with high-dose irradiation for primary or metastatic brain neoplasms. Symptoms include headache, vomiting, altered mental state, and worsening of pre-existing neurologic dysfunction. This syndrome is due to increased intracranial pressure. It can be treated with high-dose corticosteroids, which are frequently administered before initiating radiation therapy. Early delayed syndrome consists of gradual development of encephalopathy or other signs that can simulate neoplasm progression; however, this can resolve spontaneously. Late delayed radiation-induced syndrome occurs months or years after completion of radiation therapy. This is due to radiation-induced necrosis. The CT/MRI can show findings simulating recurrent neoplasm; differentiation for radiation necrosis from recurrent neoplasm; differentiation of radiation necrosis from recurrent neoplasm can only be established by pathologic findings obtained from surgery or autopsy.
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