Neurologic Complications of Pediatric Cardiac, Gastrointestinal, and Renal Diseases

JAVIER L. SANCHEZ, MD; GARY B. ZUCKERMAN, MD; and EDWARD E. CONWAY, JR., MD, MS FAAP, FCCM

Systemic diseases can have devastating consequences on the homeostasis of the nervous system. Disturbances of the central and peripheral nervous systems may result in severe neurologic dysfunction, increasing the morbidity and mortality of patients with systemic disease processes. This review presents an overview of several common systemic diseases in children, which may exhibit neurologic signs and symptoms: congenital heart disease, gastrointestinal disorders, and hepatic and renal failure. The primary care physician is often times the first to encounter such neurologic signs and symptoms and must, therefore, be aware of their implications in the context of the underlying illness.

**Educational Objectives**

1. Recognize the neurologic signs and symptoms of various chronic pediatric conditions.
2. Discuss the proposed etiologies of neurologic findings in various respective chronic conditions of childhood.
3. Emphasize the role of the general pediatrician in the co-management of neurologic conditions in children with chronic disease.

**Neurologic Complications Associated with Congenital Heart Disease**

Each year, roughly 26,000 children are born with congenital heart disease (CHD). The overall survival of children with congenital heart disease has markedly increased over the past 25 years. As more of these children survive, various sequelae of congenital heart disease may be encountered. In this regard, neurologic complications of congenital heart disease...
are becoming increasingly recognized.

Neurologic sequelae associated with congenital heart disease may arise as a complication or feature of the congenital heart lesion, or as a result of invasive treatments (surgery, catheterization) a patient may undergo. Neurologic complications of congenital heart disease are summarized in Table 1.

**Intellectual Dysfunction**

Children with cyanotic congenital heart disease have historically performed less well on IQ testing than age-matched normal controls. Chronic hypoxia has been suggested to be a significant contributing factor. Children with cyanotic congenital heart lesions had lower IQ scores than children with non-cyanotic congenital heart lesions and those with normal hearts. Of interest was that children with non-cyanotic heart lesions performed less well on IQ tests than healthy children. The duration of hypoxia has been shown to be significantly associated with the degree of intellectual dysfunction in children with tetralogy of Fallot. Children who had palliative procedures performed at early ages had significantly higher IQ scores than children who had palliative procedures performed when they were older. Similarly, children who underwent palliative procedures for transposition of the great vessels during infancy performed higher on IQ tests than age-matched patients who had palliative procedures performed after 4 years of age.

**Neuropsychological Dysfunction**

The association between congenital heart disease and neuropsychological dysfunction is unclear. Children with asymptomatic congenital heart disease have been reported to be self-indulgent, dependent, overprotected, and lacking in ambition. No association was noted between the degree of neuropsychologic dysfunction and the severity of previous cardiac-related symptomatology. Other reports, however, claimed that children with cyanotic congenital heart disease were not more likely to have an emotional or psychological disorder in the absence of other factors such as intellectual or neuropsychologic impairment. Children with congenital heart disease have been noted to have an increased incidence of school-related problems, low self-esteem, and clinical depression. Long-term psychological studies suggest that adults with congenital heart disease have higher than normal amounts of emotional stress.

Therefore, children with congenital heart disease (cyanotic and acyanotic) appear to have evidence of intellectual and neuropsychological dysfunction that is often independent of the severity of their heart defects. Early intervention may prove beneficial to the increasing number of survivors with congenital heart disease.

**Cerebrovascular Accidents**

Cerebrovascular accidents (strokes) that are not related to invasive diagnostic or therapeutic cardiovascular procedures have been reported in children with congenital heart disease. (The reader is referred to the article by Mendoza and Conway in this issue of Pediatric Annals.) When strokes occur, the results can be both dramatic and devastating. The majority of non-procedure-related strokes occurring in children with congenital heart disease occur in patients with cyanotic heart lesions. Most of these strokes are related to venous thromboses. The majority of children are under 4 years of age.

Pediatric congenital heart disease patients who develop stroke often present with hemiplegia. These children may also present with lethargy, seizures, bilateral hemiplegia, or signs of brainstem dysfunction or increased intracranial pressure. Recent findings, based on computed tomography (CT) and magnetic resonance imaging (MRI), indicate that clinically silent strokes may occur in children with congenital heart disease. The long-term clinical implications of these asymptomatic strokes is unclear. Strokes have been associated with preceding events such as febrile illnesses and cyanotic attacks. However, often there is no identifiable precipitating event.

The etiology and pathogenesis of non-procedure-related cerebrovascular disease is unclear. Predisposing conditions include increased blood viscosity, paradoxical emboli associated with right to left intracardiac shunts, and noninfectious endocarditis. Iron deficiency, despite normal or elevated hemoglobin levels, may be a predisposing factor leading to venous thromboses. In children under 4 years of age, iron deficiency and hypoxemia may be important etiologic factors of thromboses. In older patients, polycythemia and hypoxemia are thought to be contributing factors. It has been postulated that iron deficiency results in microcytosis. The microcytes are less deformable than normocytes (normal size red
blood cells). Patients with cyanotic congenital heart disease are usually polycythemic. The combination of microcytosis and polycythemia is believed to result in increased red cell viscosity and decreased deformity, leading to an increased predilection for clotting and thrombosis. 

A variety of unusual stroke syndromes have been associated with coarctation of the aorta. A "migraine-like" syndrome has been reported in patients with coarctation of the aorta. These patients present with migraine headaches. (The reader is referred to the article by Molofsky on headaches in this issue of Pediatric Annals.) Many patients also complain of pain, cramps, and paresthesia in the lower extremities. Vascular insufficiency may be the etiology of these symptoms. Patients with coarctation of the aorta have an increased incidence of cerebral aneurysms and systemic hypertension. These patients may present with stroke secondary to rupture of cerebral aneurysms. Presenting signs and symptoms include hemiplegia, coma, and meningismus. If coarctation of the aorta is associated with a deformity of the aortic valve, patients may also be subjected to embolic-related strokes.

Patients with coarctation of the aorta may also experience cerebral vascular accidents involving the spinal cord. The etiology is believed to be due to compression of either the anterior spinal artery or the spinal cord by vascular aneurysms or rupture of an aneurysm with resultant cord compression from a hematoma. Patients present with signs and symptoms of spinal cord ischemia including paraparesis or paraplegia.

Management of a cerebrovascular accident in a child with congenital heart disease depends on prompt recognition of the signs and symptoms of stroke. A child with congenital heart disease who presents with any neurologic deficits or symptoms should be suspected to have had a cerebrovascular accident. Diagnosis is made from the clinical presentation and either CT or MRI evidence of a cerebrovascular accident. Once the diagnosis of stroke has been made, consultations from pediatric cardiologists, neurologists, and neurosurgeons may help guide further management.

Brain Abscess

Brain abscesses are associated with congenital heart disease and can result in significant morbidity and mortality in affected children. Although abscesses may also develop in children with other forms of congenital heart disease, most commonly brain abscesses occur in children with transposition of the great vessels and tetralogy of Fallot. The pathogenesis is as follows. Normally, the lungs serve as filters for blood as blood passes from the right side of the heart through the lungs en route to the left side of the heart. In various forms of congenital heart disease, right-to-left intracardiac shunting of blood occurs. The filtering function of the lungs is bypassed, and bacteria may gain entry to the central nervous system (CNS). As stated above, children with congenital heart disease are subject to brain infarction (often asymptomatic) which results in necrotic brain tissue. Necrotic brain tissue may serve as growth media for the unfiltered bacteria, resulting in abscess formation. Bacteria commonly associated with brain abscesses in children with congenital heart disease include Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumoniae, and anaerobes.

Abscess formation usually occurs in children older than 2 years. They present with fever, lethargy, irritability, seizures, focal signs depending on the location of the abscess, and signs of increased intracranial pressure. One third of patients with brain abscesses may present with a clinical picture suggestive of stroke. Brain infarction can result in brain necrosis. Bacteremia can then result in abscess formation. Following imaging studies, a neurosurgical consultation should be obtained to guide further management. Antibiotics directed toward the microorganisms described above should be administered.

NEUROLOGIC ABNORMALITIES ASSOCIATED WITH CONGENITAL HEART DISEASE

Certain CNS abnormalities have been associated with congenital heart disease. An association between the hypoplastic left heart syndrome and neurologic abnormalities such as ocular defects, microcephaly, abnormal mantle formation, agenesis of the corpus callosum, and holoprosencephaly has been noted. A variety of ocular abnormalities occurring in children with congenital heart disease has been reported. These defects include strabismus, amblyopia, and refractive abnormalities. An increased incidence of hearing loss in children with congenital heart disease has been reported. The cause of these associated neurologic abnormalities in children with congenital heart disease has not been elucidated. These neurologic defects occur in children who do not have multiple malformation syndrome or chromosomal abnormalities. In addition, these children often have no history of exposure to teratogens or intrauterine infections. An underlying common etiologic agent for congenital cardiac and neurologic defects has not been identified.

NEUROLOGIC COMPLICATIONS RELATED TO INVASIVE PROCEDURES

Invasive procedures, such as cardiac catheterization, curative and palliative surgery, and heart transplantation, have greatly aided the management of congenital heart disease in children. These procedures, however, have been associated with neurologic complications.
Cardiac Catheterization
Most neurologic complications related to cardiac catheterization are believed to be due to cerebral emboli. Often these emboli result in no symptoms, though patients at risk are those with right-to-left intra cardiac shunts in whom the filtering capacity of the lungs is bypassed. Neurologic complications from cardiac catheterization may at times produce symptoms. Stanger and colleagues reported on two patients who developed focal paresthesias, and Cohn and colleagues described two who developed seizures following cardiac catheterization. Both groups of investigators reported the symptoms to be transient. Cerebral embolization may very well have contributed to these complications.

Cardiac Surgery
The mortality associated with surgical repair of congenital heart defects has fallen dramatically. As survival rates have increased, some investigators have raised the concern that more children will develop neurologic complications related to cardiac surgery. Neurologic morbidity after open heart surgery on young infants may be due to several factors, including the type of lesion, preexisting brain abnormalities, duration of deep hypothermia, and strokes.

Children who underwent surgery for aortic arch anomalies were noted to have a higher incidence of neurologic complications than children with other congenital heart defects.

Also an association between episodes of low mean arterial pressure during the intra or postoperative period and subsequent neurologic morbidity has been reported. Further, the length of time of deep hypothermic circulatory arrest has been reported to be directly proportional to the development of postoperative neurologic complications. Finally, during the immediate postoperative period, an acute encephalopathic syndrome has been described consisting mainly of altered sensorium (not attributed to anesthesia) and seizures. Usually the acute postoperative encephalopathy is transient and self-limited; however, chronic sequelae have been reported.

These persistent neurologic sequelae following the acute encephalopathy syndrome in children with surgical correction of congenital heart defects have included mental retardation, seizure disorders, learning disabilities, cerebral palsy, and persistent vegetative states. The development of behavioral disorders, attention deficits, speech deficits, seizures, global developmental delay, and hypotonia as long-term chronic sequelae of pediatric open heart surgery has also been reported as well as visual and ocular disorders.

Cerebrovascular accidents have been described as complications of open heart surgery in children. Cranial ultrasound on infants before and after heart surgery revealed new postoperative intracranial hemorrhages and infarctions in some of these infants. And cerebellar infarctions have been a postoperative complication of the Fontan procedure.

The development of a choreoathetoid movement disorder has been described in children following open heart surgery. Its severity and degree of improvement varies among patients. Length and degree of hypothermia is related to choreoathetosis in children undergoing open heart surgery. This complication appears to solely involve pediatric open heart patients. The etiology, physiology, and treatment of this postoperative neurologic complication remains to be elucidated.

Heart Transplantation
Heart transplantation has been used increasingly for children with certain severe forms of congenital heart disease (e.g., hypoplastic left heart syndrome) and end-stage cardiomyopathy. As the survival rate for children undergoing heart transplantation improves, more will exhibit neurologic complications from transplantation. Neurologic complications have been reported in 40% to 50% of children who undergo heart transplantation. These include intracranial hemorrhage, seizures, hypotonia, global developmental delay, and dysmetria. The etiology of these complications is unclear. Hypertension, emboli, hypoxia, ischemia, and medication interactions have been postulated as etiologies.

The Role of the Pediatrician
In conclusion, congenital heart disease remains a significant problem in the pediatric patient population. As the survival rate of patients with congenital heart disease has increased, more children will be presenting with neurologic problems. These may be the result of the heart disease, or a sequelae of invasive diagnostic or therapeutic procedures. Health care providers involved in the care of children with congenital heart disease should be aware of the various neurologic complications of congenital heart disease.

The pediatrician who is involved with managing a child with a chronic neurologic condition related to open heart surgery should carefully review the anesthetic, intraoperative, and postoperative notes from the child's hospitalization. A management plan should be instituted and coordinated between the primary care physician, pediatric cardiologist, and pediatric neurologist to optimize the patient's ongoing care.

NEUROLOGIC COMPLICATIONS OF GASTROINTESTINAL DISEASES
Gastrointestinal diseases associated with neurologic derangements include hepatic failure, inflammato-
ry bowel disease, short gut syndrome, celiac disease, and tropical sprue. Neurologic complications of gastrointestinal diseases may be caused by an inability to metabolize neurotoxic products (hepatic failure), or by malabsorption of essential nutrients (inflammatory bowel disease, short gut syndrome, celiac disease, and tropical sprue). The buildup of toxic substances or the deficiency of micronutrients can result in profound neurologic abnormalities with increased morbidity and mortality.

**Hepatic Failure**

The liver plays an important role in maintaining the homeostasis of the nervous system. It is primarily responsible for regulating substrate availability through synthetic regulatory functions on carbohydrate, protein, and lipid metabolism. It also plays a major role in the biotransformation and excretion of toxic metabolites. There are fewer than 2,000 cases of hepatic failure per year. The most common cause of hepatic failure remains viral infection, namely hepatitis A, B, and C, followed by drug-induced liver failure and congenital conditions.54

One of the most serious complications of liver dysfunction is hepatic encephalopathy. It is characterized as a neuropsychiatric disorder with symptoms of gross personality changes, depression, and irritability in the early stages. Hepatic encephalopathy may progress to more severe neurologic and psychologic complications in later stages.35 The pathogenesis of this condition is poorly understood. Multiple theories have been proposed to explain the clinical picture. The failure of the biotransformation and excretory functions of the liver is believed to contribute to hepatic encephalopathy. The most widely studied toxin in hepatic encephalopathy is ammonia. Hyperammonemia interferes with cerebral function during both hepatic failure and in patients with urea cycle enzyme defects. Therapy aimed at reducing ammonia levels in urea cycle defects ameliorates hepatic encephalopathy.35 However, levels of ammonia do not correlate with neurologic findings during hepatic encephalopathy of other etiologies. Recent research has concentrated on the role of elevated gamma-amino-butyric acid (GABA) levels.36 GABA is an amino acid neurotransmitter synthesized from glutamine. A GABA-benzodiazepine receptor has been postulated to exist in the CNS. The binding of GABA with the GABA receptor causes inhibitory tone in the cells of the CNS and this may contribute to the encephalopathy. Since binding of benzodiazepines with the GABA receptor further increases this inhibitory state, benzodiazepines are not recommended in the management of agitation in hepatic encephalopathy.

The neurologic signs and symptoms of hepatic encephalopathy have been grouped into four stages (Table 2). Signs and symptoms of stage I are subtle and are often not recognized. Stage II is characterized by the presence of asterixis, a flapping tremor of the upper extremities. During this stage the patient's neurologic condition continues to deteriorate. Patients become lethargic and disoriented. As the patient progresses to stage III, seizures may develop. Speech is incomprehensible and incontinence may occur. Stage IV patients become comatose. They often respond to pain with decerebrate or decorticate posturing.37 Imaging studies of the brain will show the presence of cerebral edema. The patient may die if therapy is not instituted. The comatose stage in stage IV is sometimes reversible if liver function is restored.

Liver transplantation is often a treatment option in cases of irreversible hepatic failure. The pediatrician should be familiar with the signs of liver failure and consult hepatic specialists early to anticipate the possible need for transplantation.

Liver transplantation has gained wide acceptance as a treatment for end stage liver failure. Current studies show a 1-year survival rate greater than 80%. Neurologic complications occur in over 80% of adults with liver transplantation. These complications associated with liver transplantation include seizures (from electrolyte disturbances or toxic effect of

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mental Status/Behavior</th>
<th>Motor Reflexes</th>
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<tbody>
<tr>
<td>I</td>
<td>Anxiety</td>
<td>Fine postural tremor</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
<td>Asterixis</td>
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<tr>
<td></td>
<td>Agitation</td>
<td>Primitive reflexes</td>
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<tr>
<td></td>
<td>Altered sleep patterns</td>
<td>suck, grasp</td>
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<tr>
<td></td>
<td>Depression</td>
<td>Ataxia</td>
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<tr>
<td></td>
<td></td>
<td>Gross personality changes</td>
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<td></td>
<td></td>
<td>Disorientation (time)</td>
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<td></td>
<td></td>
<td>Inappropriate behavior</td>
</tr>
<tr>
<td>II</td>
<td>Drowsiness</td>
<td>Hyperreflexia</td>
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<tr>
<td></td>
<td>Lethargy</td>
<td>Seizures</td>
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<td></td>
<td></td>
<td>Babinski's sign</td>
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<td></td>
<td></td>
<td>Hyperventilation</td>
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<td></td>
<td></td>
<td>Incontinence</td>
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<td></td>
<td></td>
<td>Hypothermia</td>
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<tr>
<td></td>
<td></td>
<td>Myoclonus</td>
</tr>
<tr>
<td>III</td>
<td>Stupor, confused</td>
<td>Hyperreflexia</td>
</tr>
<tr>
<td></td>
<td>Asterixis</td>
<td>Seizures</td>
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<tr>
<td></td>
<td>Disorientation: time</td>
<td>Babinski's sign</td>
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<td>and place</td>
<td>Hyperventilation</td>
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<td></td>
<td>Somatic but arousable</td>
<td>Incontinence</td>
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<td></td>
<td>Seizures</td>
<td>Hypothermia</td>
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<td>IV</td>
<td>Coma</td>
<td>Decerebrate</td>
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<tr>
<td></td>
<td></td>
<td>posturing</td>
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<td>Brisk</td>
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<td></td>
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<td>oculocephalic reflexes</td>
</tr>
</tbody>
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TABLE 3

Neurologic Manifestations of Micronutrient and Electrolyte Deficiencies

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Manifestation</th>
</tr>
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<tbody>
<tr>
<td>Electrolytes</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>Seizures</td>
</tr>
<tr>
<td>Potassium</td>
<td>Areflexic paralysis</td>
</tr>
<tr>
<td>Vitamins</td>
<td></td>
</tr>
<tr>
<td>Thiamine (B1)</td>
<td>Polynephropathy</td>
</tr>
<tr>
<td>Niacin (B3)</td>
<td>Dementia</td>
</tr>
<tr>
<td>Pyridoxine (B6)</td>
<td>Seizures, neuropathy</td>
</tr>
<tr>
<td>Cyanocobalamin</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>E</td>
<td>Areflexia, ataxia</td>
</tr>
<tr>
<td>Minerals</td>
<td></td>
</tr>
<tr>
<td>Chromium</td>
<td>Neuropathy</td>
</tr>
<tr>
<td>Iodine</td>
<td>Neurologic cretinism</td>
</tr>
<tr>
<td>Copper</td>
<td>Pseudoparalysis</td>
</tr>
<tr>
<td></td>
<td>Ataxia</td>
</tr>
</tbody>
</table>

cyclosporine or tacrolimus), encephalopathy, and cerebral vascular accidents.38 Central pontine myelolysis (CPM) occurs in up to 19% of liver transplantation patients. CPM is a non-systemic, non-inflammatory demyelination process. It is thought to occur secondary to rapid changes in serum sodium concentrations, which occur during the intra- or postoperative period. The long-term management of liver transplantation patients is complex and requires close consultation between the general pediatrician and the transplant center.

Reye Syndrome

Reye syndrome is a rare but well-described acute encephalopathy associated with cerebral edema, hypoglycemia, coagulopathy, and hyperammonemia. Many believe the decreasing incidence of Reye syndrome is related to reduced use of salicylates in children during febrile illness. Typically, Reye syndrome presents during the recovery phase of an acute illness. An association exists between Reye syndrome and the use of salicylate-containing compounds in the treatment of children with varicella or influenza A and B.39 The development of Reye syndrome is heralded by the onset of protracted vomiting, followed by mental status changes. These mental changes have been used to categorize the illness into 5 distinct stages. The first stage is associated with vomiting and lethargy. Laboratory tests will show some degree of liver dysfunction. During stage II, the patient becomes confused and combative. Stage III is characterized by the onset of seizures. During stage IV, decerebrate posturing and deepening coma are observed. Stage V, often irreversible, is characterized by fixed and dilated pupils, loss of deep tendon reflexes, and respiratory arrest. Symptomatology is closely tied to worsening liver failure and mitochondrial dysfunction. If untreated, cerebral edema and death may ensue.

Wilson's Disease

Wilson's disease is caused by a defect in copper metabolism that results in copper deposition in multiple tissues. Systems affected include the liver, kidneys, eyes, hair, and CNS. The disease is inherited as an autosomal recessive gene.40 The clinical manifestation of Wilson's disease includes hepatic disease—acute hepatitis, fulminant hepatitis, or cirrhosis—and neurologic manifestations.41 Neurologic symptoms occur in 40% of patients with Wilson's disease, often appearing during adolescence. These symptoms include tremors, gait instability, psychiatric disorders, and seizures. The clinical diagnosis of Wilson's disease includes (1) presence of Kaiser-Fleisher rings, (2) a low serum ceruloplasmin concentration, (3) an elevated tissue copper concentration found in liver biopsy, and (4) an elevated urine copper concentration. The treatment of Wilson's disease requires the prompt initiation of chelating agents. Penicillamine is the therapy of choice for binding copper and promoting renal excretion. The pediatrician should consider Wilson's disease (and Reye syndrome) in the patient with encephalopathy and signs of hepatic pathology.

Malabsorption of micronutrients often occurs in gastrointestinal diseases. Resultant micronutrient deficiencies may cause neurologic symptomatology. A variety of neurologic manifestations of specific micronutrient deficiencies is summarized in Table 3.

Inflammatory Bowel Disease

The pathogenesis of inflammatory bowel disease (IBD) remains unknown. Its two major clinical forms, ulcerative colitis and Crohn's disease, are characterized by a chronic, relapsing, debilitating inflammatory process.42 The complications and extra intestinal manifestations of IBD affect multiple organ systems and can occur independently of bowel symptom exacerbation. The association of neurologic disorders with IBD is more common than appreciated, with an estimated frequency varying from less than 1% to 35%.43 This discrepancy in neurologic manifestations can be accounted for by the inclusion or exclusion of metabolic or nutritional deficiencies that occur with IBD.

The most significant neurologic manifestation in IBD is cerebrovascular accidents. Cerebral venous thromboses, with brainstem and cerebral infarctions, have been reported.44 The etiology is unclear. Cerebrovascular accidents have been estimated to occur in 4% of patients with IBD. Additional neurologic manifestations of IBD are seizures, inflammatory neuropathies, and myasthenia gravis.45 Due to the complexity of the disease and its many extra intestinal manifestations, these patients are best followed in
conjunction with a gastroenterologist.

**Short Gut Syndrome**

Surgical resection of necrotic bowel is common in very low birth weight infants who have had necrotizing enterocolitis. Other pediatric patients may also undergo extensive resections of necrotic bowel due to mid-gut volvulus, malrotations, and intussusception. The increasing rate of survival of these patients has increased the number of children with what is termed short gut syndrome. The neurologic signs and symptoms of short gut syndrome are primarily related to electrolyte abnormalities and vitamin deficiencies. They include seizures, ataxia, and cognitive impairment. These infants often require total parenteral nutrition delivered by central venous access. Their tenuous medical status and high incidence of mortality warrant close monitoring by the primary care pediatrician and pediatric gastroenterologist.

**Celiac Disease**

Celiac disease (gluten-sensitive enteropathy) is characterized by small bowel mucosal damage caused by an immunologically mediated intolerance to gluten-containing grains. This disorder is most frequently seen between 6 months and 2 years following the introduction of gluten into the diet. In Europe, it has an incidence of 1:300 births, whereas in the United States the incidence is 1:3000 births. The most common presenting symptoms are failure to thrive, diarrhea, irritability, vomiting, anorexia, and foul-smelling stools. Pathologically, villous atrophy, crypt hyperplasia, and lymphocytes in the epithelial layer characterize celiac disease. The incidence of significant neurologic manifestations has been estimated at 10%. These consist of areflexia, ataxia, myopathy, peripheral neuropathy, and seizures. Although most of the neurologic manifestations are related to malabsorption, the institution of a gluten-free diet may be ineffective in reversing neurologic changes once they are present. This is consistent with the finding that small intestine morphology may not improve after institution of gluten-free diets despite improvement in gastrointestinal symptomatology.

The neurologic alterations can be attributed to vitamin malabsorption or electrolyte disturbances. Electrolyte disturbances commonly seen in celiac disease are hypokalemia and hypocalcemia. These disturbances can result in seizures and myopathies. Correction of the electrolyte disturbances will result in prompt resolution of clinical symptoms. Myopathy and peripheral neuropathies occur secondary to vitamin malabsorption. Treatment with intravenous or intramuscular supplementation has not been successful in reversing neurologic symptoms. The best treatment for celiac disease is prompt diagnosis and institution of a gluten-free diet.

**Tropical Sprue**

The clinical and pathologic findings of tropical sprue are similar to celiac disease, however, an infectious etiology has been postulated due to its responsiveness to antibiotics. It should be suspected in patients with a history of recent travel to a tropical region. Myopathy is the most frequently encountered neurologic abnormality. It is most likely secondary to vitamin E deficiency. Treatment with antibiotics and vitamin supplementation will result in neurologic improvement.

**NEUROLOGIC MANIFESTATIONS OF RENAL DISEASE**

The kidney is the primary excretory organ in the body, and its main function is maintenance of fluid and electrolyte balance. When renal function becomes impaired to the point where body homeostasis cannot be maintained, renal failure is diagnosed. Renal failure has been divided into acute and chronic phases. Causes of renal failure can be divided into (1) anatomical (obstruction, malformation, dysplasia, and hypoplasia), (2) acquired (glomerular disease, glomerulonephritis, hemolytic uremic syndrome), and (3) hereditary disorders (Alport syndrome, cystic disease). Regardless of the cause of renal failure, the neurologic manifestations are often similar.

**Uremic Encephalopathy**

Children with chronic renal failure often present with fatigue, poor concentration, and headaches. Symptoms such as slurred speech, muscle weakness, and cramps point to a worsening of renal function. Serious complications requiring emergent recognition and management include peripheral neuropathy, seizures, and coma. The symptoms described above are consistent with uremic encephalopathy. As renal function deteriorates and glomerular filtration falls, neurologic manifestations increase. In early states of uremic encephalopathy, periods of well-being alternate with periods of lassitude. Mild headaches caused by fluid shifts between the intra and extracellular compartments are frequently noted: A decrease in intracellular fluid is seen in hyperosmolar states (ie, hypernatremia), whereas an increase in intracellular fluid and subsequent cerebral edema is seen in hypoosmolar states (ie, hyponatremia). In the presence of severe headaches, malignant hypertension should be suspected.

Asterixis, a flapping tremor of the outstretched hand described above for hepatic encephalopathy, is also frequent in uremic encephalopathy. Children with renal failure can develop focal neurologic findings such as loss of hearing, loss of vision, and nystagmus. Less common in pediatric patients with chronic renal failure are peripheral neuropathies. Older children may complain of the "burning feet syndrome." Rarely do these children exhibit progression.
to sensory loss and paralysis. Severe uremic encephalopathy can lead to psychosis, hallucinations, coma, and death if untreated. The primary care pediatrician must be able to recognize these entities to institute life-saving therapeutic interventions. These patients are best co-managed by the pediatrician and a pediatric nephrologist.

The neurologic manifestations of renal failure can be reversed with hemodialysis. This suggests dialyzable compounds cause the neurotoxic features of renal failure.54

The following substances are increased in the serum of patients with uremic encephalopathy and have been implicated as neurotoxins: urea, creatinine, urates, and organic/inorganic acids. However, attempts to reproduce the neurologic symptoms by infusing high concentrations of these substances have failed to produce similar responses. Recent evidence has implicated parathyroid hormone (PTH) as a uremic neurotoxin.55 PTH is elevated in both acute and chronic renal failure and may act directly as a neuromodulator and indirectly by increasing the amount of calcium in the brain.56 Aluminum has been shown to accumulate in the brain as a result of phosphate-binding therapy or dialysis therapy. Patients absorbed trace concentrations of aluminum present in dialysis fluids. Aluminum is thought to affect neural tissue by interfering with hoxose metabolism.57 Children with chronic aluminum intoxication have been shown to have microcephaly and mental deficiency. And aluminum encephalopathy is often fatal, even in the absence of uremia.

Hypertensive Encephalopathy

Uncontrolled hypertension, a common problem in pediatric patients with renal disease, may result in encephalopathy. The patophysiologic changes seen in hypertensive encephalopathy are necrotizing arteriolitis with blood-brain barrier disruption. The presenting symptoms are headaches, often times severe, vomiting, and confusion. Unrecognized and untreated, it progresses to convulsions, coma, and death. Hypertensive encephalopathy is a medical emergency.

IATROGENIC NEUROLOGIC COMPLICATIONS IN RENAL FAILURE PATIENTS

Dialysis therapy is associated with neurologic complications. The major characteristics are headaches, encephalopathy, seizures, and psychosis. The most likely mechanism is rapid changes in osmolarity between the intra and extracellular compartments in the CNS. Renal transplantation is also associated with neurologic problems. It has become an established treatment for end stage renal disease and constitutes the most frequently performed solid organ transplant. The neurologic manifestations of renal transplantation include cyclosporine-induced encephalopathy, seizures, and compressive femoral neuropathies.58 Compressive femoral neuropathies occur secondary to hematoma formation at the surgical site. The long-term management of renal transplant patients requires a close working relationship between the primary care physician and the nephrologist.

REFERENCES