INTRODUCTION

Many medical conditions have neurologic and psychiatric symptoms, and early identification of the underlying cause can be critical in directing further management (Table 1). Medical conditions known to cause neuropsychiatric symptoms can also be varied in presentation, making diagnosis challenging. The number of medical conditions that potentially cause neurologic and psychiatric symptoms is extensive. This...
article highlights several broad categories of medical diseases (infectious, autoimmune, endocrinologic, metabolic, and neoplastic), with a focus on pragmatic considerations in evaluation, diagnosis, and management in the primary care setting. The focus of this article is on common medical conditions with neuropsychiatric manifestations, as well as specific diseases that have a characteristic neuropsychiatric presentation requiring early detection and evaluation.

### INFECTIOUS

**Human Immunodeficiency Virus**

Human immunodeficiency virus (HIV) disease can cause neuropsychiatric manifestations as a result of primary HIV disease, opportunistic infections and malignancies, medication side effects, and the psychosocial consequences and stigma associated with HIV infection. Common neuropsychiatric disorders that are associated or comorbid with HIV disease include minor cognitive impairment and dementia; delirium; peripheral nervous system disorders such as polyneuropathy; and psychiatric syndromes such as bipolar affective disorder, major depression, schizophrenia, and substance abuse. Cognitive impairment in the setting of HIV infection can be caused by

<table>
<thead>
<tr>
<th>System</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>HIV/AIDS</td>
</tr>
<tr>
<td></td>
<td>• Opportunistic infections/malignancies</td>
</tr>
<tr>
<td></td>
<td>• Syphilis</td>
</tr>
<tr>
<td></td>
<td>• Lyme disease</td>
</tr>
<tr>
<td></td>
<td>• Prion disease</td>
</tr>
<tr>
<td>Rheumatologic/autoimmune</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td></td>
<td>Vasculitides</td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Endocrinologic</td>
<td>Hypothyroidism/hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td>Hypoparathyroidism/hyperparathyroidism</td>
</tr>
<tr>
<td></td>
<td>Cushing syndrome</td>
</tr>
<tr>
<td></td>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Vitamin deficiencies</td>
</tr>
<tr>
<td></td>
<td>• Thiamine (vitamin B₁)</td>
</tr>
<tr>
<td></td>
<td>• Vitamin B₁₂</td>
</tr>
<tr>
<td></td>
<td>Micronutrient abnormalities</td>
</tr>
<tr>
<td></td>
<td>• Hypocalcemia/hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>Acute hepatic porphyrias</td>
</tr>
<tr>
<td></td>
<td>Wilson disease</td>
</tr>
<tr>
<td></td>
<td>Amyloidosis</td>
</tr>
<tr>
<td></td>
<td>Hepatic encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Uremia</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Paraneoplastic syndromes</td>
</tr>
<tr>
<td></td>
<td>CNS tumors (primary and metastatic)</td>
</tr>
<tr>
<td></td>
<td>Carcinomatous meningitis</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Sickle cell disease (cerebrovascular disease)</td>
</tr>
<tr>
<td>Heritable/genetic</td>
<td>Huntington disease</td>
</tr>
<tr>
<td></td>
<td>Lysosomal storage diseases</td>
</tr>
</tbody>
</table>

*Abbreviations: AIDS, acquired immunodeficiency syndrome; CNS, central nervous system; HIV, human immunodeficiency virus.*
encephalopathy attributed to the virus; central nervous system (CNS) lymphoma; and primary CNS infections such as progressive multifocal leukoencephalopathy (PML), cryptococcal meningitis, toxoplasmosis, and cytomegalovirus (CMV) encephalitis.

HIV-associated neurocognitive disorders (HAND), can be classified as asymptomatic neurocognitive impairment, mild neurocognitive disorder, or HIV-associated dementia, with HIV-associated dementia being the most severe, characterized by profound abnormalities in neuropsychological testing and significant impairment in a patient’s ability to perform activities of daily living. Some degree of neurocognitive impairment has been found to be present in between a quarter and half of all patients infected with HIV in one large study, although other studies have found the rate of cognitive impairment in patients with early stage HIV and high viral loads to be similar to that in HIV-negative individuals.3 HAND is characterized by the triad of memory impairment, mood (depressive) symptoms, and movement disorders such as ataxia, tremor, weakness, and bradykinesia.6 Screening for HAND in patients infected with HIV includes neuropsychological testing, and is a diagnosis of exclusion made after alternate causes have been ruled out. Treatment includes antiretroviral (ARV) medications, medications intended to manage symptoms, such as stimulants and antipsychotics,7 and supportive care (including psychiatric care and attention to functional needs with rehabilitation services).

PML, a demyelinating disease that affects the CNS, is caused by the opportunistic reactivation of polyomavirus (JC virus) infection. PML occurs in immunosuppressed patients, and, before the advent of ARV therapy, affected up to 5% of patients with advanced HIV disease.8 The disease is far less prevalent since the broader use of ARVs. PML has historically been thought of as a disease of the white matter (specifically affecting oligodendrocytes and astrocytes) but it can also affect structures such as the cortical gray matter, thalamus, and basal ganglia.9 It rarely affects the spinal cord.10 Classic symptoms include weakness, sensory changes, cognitive dysfunction, ataxia, visual symptoms such as hemianopsia and diplopia, aphasia, and seizures.9 Definitive diagnosis can be made by brain biopsy, but can also be made by using polymerase chain reaction to show the presence of JC virus in the cerebrospinal fluid (CSF) and by the characteristic demyelinating lesions seen on neuroimaging. The prognosis for patients with PML is poor, with a median survival in patients affected by HIV of 1.8 years in the post-ARV era. Prognosis is improved in patients with higher CD4 counts.11 Treatment is focused on optimizing ARV therapies and although several specific treatment agents have been studied, there are no large-scale, robust data to support the use of these agents, and there is no treatment currently available that is designed to treat JC virus specifically.12,13

Cryptococcal meningitis is a protozoan infection that affects immunocompromised patients, including patients with advanced HIV/acquired immunodeficiency syndrome. Symptoms typically present insidiously and subacutely, with headaches, mental status changes, lethargy, and memory loss developing over a period of weeks. Diagnosis is made using lumbar puncture, which highlights the importance of a high index of suspicion in susceptible patients given that the diagnosis cannot be made from serology alone. Patients with cryptococcal meningitis classically have a markedly high opening pressure. CSF examination can be significant for low glucose and high protein levels, and cell counts are typically low when the infection is HIV associated. Cryptococcal meningitis is treated with antifungals including amphotericin B, flucytosine, and flucnazole, and is fatal if untreated.13

Toxoplasmosis gondii is a protozoan disease that is usually a manifestation of reactivation of latent cysts in immunosuppressed patients (typically patients with HIV with CD4 counts <100) and is also an important pathogen in pregnant women.
Toxoplasmosis in HIV-positive patients classically presents with headache, fever, and mental status changes, although focal neurologic symptoms and seizures are also common. Extracerebral manifestations can include posterior uveitis and pneumonitis. Diagnosis is made from serologies (positive antitoxoplasma immunoglobulin G), imaging, and a clinical presentation suggesting toxoplasmosis. Definitive diagnosis can be made by biopsy of a suspected lesion. First-line treatment includes sulfadiazine, pyrimethamine, and leucovorin.¹³

Ventriculoencephalitis related to CMV infection has declined since the advent of effective ARV treatments. CMV can affect various parts of the neurologic system and, when the brain is involved, classically presents subacutely with altered mental status, and commonly with memory impairment.¹⁴ Diagnosis is made by isolating CMV antigen or DNA from the CSF, and imaging is also used to rule out other potential pathogens/causes.¹⁵,¹⁶ Treatment of CMV encephalitis includes ganciclovir and foscarinet,¹⁷ although the data supporting this treatment are limited to case reports and small, nonrandomized prospective studies.¹⁸ Prognosis is poor and CMV infection is rapidly fatal, regardless of treatment.¹⁹

**Syphilis**

Neurosyphilis was once common, occurring in up to 40% of patients with documented syphilis²⁰ in the era before the advent of antibiotics. It is now rare, with the reduction attributed not just to increased treatment of early syphilis but also to the widespread prevalence of antibiotics in society and in the environment, outside the setting of specific treatment of bacterial illness in humans. Neuropsychiatric symptoms caused by syphilis are usually late manifestations of the disease. Early neurosyphilis can be either asymptomatic (diagnosed based on CSF studies) or symptomatic, presenting with acute meningitis, sometimes with leptomeningeal spread and the development of focal areas of CNS inflammation (gummas), ophthalmologic symptoms (uveitis), otic symptoms (hearing loss), and meningovascular symptoms. Many patients clear syphilitic meningitis spontaneously, whereas others develop chronic asymptomatic CNS disease, and this latter group of patients is at the highest risk for late neurosyphilis. Late neurosyphilis can present with a variety of clinical CNS syndromes, including dementia, paresis, and locomotor ataxia (tabes dorsalis). Neurosyphilis is diagnosed based on clinical presentation (history and physical examination, which can reveal characteristic abnormalities such as the Argyll-Robertson pupil in the setting of tabes dorsalis) and CSF or serum evaluation. No single laboratory test can diagnose neurosyphilis. Laboratory evaluation in a patient without known syphilis begins with nontreponemal serum testing (such as rapid plasma reagin or venereal disease research laboratory [VDRL]), and confirmed by specific treponemal testing.²¹ In patients with late neurosyphilis, nontreponemal serum testing can sometimes be falsely negative,²² although typically specific treponemal testing remains positive, making it an important part of diagnosis in patients for whom providers have a high suspicion for neurosyphilis. In patients with known prior syphilis or positive serum treponemal testing, lumbar puncture should be:

- Considered in patients with an unknown syphilis history who have neurologic or ophthalmologic symptoms consistent with neurosyphilis, and HIV-positive patients with a known history of syphilis even without symptoms of neurologic or ophthalmologic involvement
- Performed in patients with neurologic or ophthalmologic symptoms or signs with a known history of syphilis
- Performed in patients with active tertiary syphilis affecting other organ systems
- Performed in patients with documented evidence of treatment failure²³
CSF VDRL is very specific for neurosyphilis, but has a low sensitivity, meaning that a positive test is diagnostic, but a negative test may not rule out the disease. Other CSF parameters may be helpful in suggesting the diagnosis as well; an increased cell count and protein level. In HIV-positive patients, the CSF VDRL can be falsely negative, so there may be a role for a more sensitive but less specific test of the CSF (such as the fluorescent treponemal antibody absorption). Treatment of neurosyphilis requires parenteral antibiotics capable of crossing the blood-brain barrier: either intravenous (IV) penicillin G for 10 to 15 days, or procaine penicillin G intramuscularly and oral probenecid for 10 to 14 days. Ceftriaxone and doxycycline may be reasonable alternatives in patients who are allergic to penicillin.

**Lyme Disease**

Another spirochete infection, Lyme disease, caused by *Borrelia burgdorferi* and spread through the bite of the *Ixodes* tick, can present with dermatologic, musculoskeletal (joint), and neurologic manifestations. Spirochetes seed the nervous system through hematogenous spread and can cause a variety of neurologic symptoms that can be classified either by anatomic location (central vs peripheral) or time of onset (early disease, occurring within weeks or months of the initial tick bite, or late/chronic disease, with onset months to years later).

Many patients, and most of those who present with erythema migrans, can have nonspecific symptoms that are seemingly neuropsychiatric in origin, including fatigue, headache, and cognitive impairment. These ill-defined symptoms are not thought to be manifestations of CNS Lyme disease or nervous system damage and are common across patients with other inflammatory and infectious diseases (and in patients without known medical disease as well). Approximately 15% of patients develop meningitis, cranial neuropathies, or radiculopathy/radiculitis acutely, with these three sequelae constituting the classic triad for acute, early neuroborreliosis. Peripheral neuropathies (including radiculopathy, symmetric polyneuropathies, and carpal tunnel syndrome) and encephalomyelitis can occur either early in the disease course or much later, even months or years after initial infection. Diagnosis depends on a known exposure (through the bite of the *Ixodes* tick); objective clinical evidence of nervous system involvement; and laboratory data, specifically positive Lyme serologies and anti-*Borrelia* antibodies in the CSF, although anti-*Borrelia* antibodies are not required for diagnosis. Evaluation of the CSF in the setting of Lyme meningitis typically reveals a modest, lymphocyte-predominant pleocytosis, moderately increased protein, and normal glucose levels. Electromyogram/nerve conduction studies can be helpful to characterize peripheral nervous systems disorders as well. Treatment regimen and course depend on the timing and location of disease and ranges as follows:  

- Early disseminated disease with cranial nerve symptoms: oral antibiotics (doxycycline) for 2 to 4 weeks  
- Early disseminated disease with meningitis: IV antibiotics (ceftriaxone) for 4 weeks  
- Late disseminated disease with neurologic symptoms: IV antibiotics (ceftriaxone, cefotaxime, penicillin G) for 4 weeks

**RHEUMATOLOGIC**

Several autoimmune/rheumatologic diseases can cause neuropsychiatric symptoms, including, but not limited to, systemic lupus erythematosus (SLE), sarcoidosis, CNS vasculitis, and multiple sclerosis. This article focuses specifically on SLE and sarcoidosis.
Most patients with SLE develop neuropsychiatric symptoms,29 typically within the first year of diagnosis.30 Neurologic sequelae are included as a potential criterion for SLE diagnosis in both the original American College of Rheumatology diagnostic criteria31,32 and also the revised criteria proposed by the Systemic Lupus International Collaborating Clinics.33 The American College of Rheumatology divides neuropsychiatric manifestations of SLE into central and peripheral syndromes (see Table 2 for details)34 and has case definitions for each syndrome. Central syndromes can range from mild to severe, including (from most to least common) cognitive dysfunction, headaches, mood disorders, cerebrovascular disease, seizure disorders, and psychosis.35 Peripheral syndromes include, but are not limited to, Guillain-Barré syndrome, peripheral neuropathies, and myasthenia gravis, with polyneuropathies being the most common.35 The specific pathophysiologies underlying these various syndromes are varied. Medications used to treat SLE, such as steroids, can commonly cause symptoms such as psychosis and cognitive dysfunction, so considering iatrogenic causes is also imperative. Cognitive dysfunction may occur in patients with SLE and underlying psychiatric disorders or without any psychiatric history and can also be associated with CNS emboli in the setting of antiphospholipid antibodies.

Some biomarkers seem to be increased in patients with neuropsychiatric SLE,36 and associations have been found between increased levels of antineuronal antibodies and other antibodies and both neuropsychiatric symptoms generally, and cognitive defects specifically.37,38 These tools remain nonspecific in diagnosis. In addition, imaging for structural brain changes can be a helpful adjunctive tool for evaluation. SLE as a cause for neuropsychiatric symptoms remains a diagnosis of exclusion made after other potential causes have been evaluated and ruled out.

Treatment of neuropsychiatric lupus varies depending on the specific symptoms. Steroids and immunosuppressants such as azathioprine and cyclophosphamide are mainstays of treatment of lupus psychosis, as are symptom-directed treatments such as antipsychotic medications. For other neuropsychiatric symptoms such as cognitive dysfunction that can have variable underlying causes even in the setting of SLE, treatments are directed at the underlying cause: reduction or discontinuation of steroid medications if indicated, and, conversely, treating with steroid medications if the cause is thought to be antibody mediated, and/or anticoagulation if associated

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central and peripheral syndromes in neuropsychiatric SLE</strong></td>
</tr>
<tr>
<td><strong>Peripheral</strong></td>
</tr>
<tr>
<td>Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
</tr>
<tr>
<td>Cranial neuropathy</td>
</tr>
<tr>
<td>Mononeuropathy (single or multiplex)</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Plexopathy</td>
</tr>
<tr>
<td>Polyneuropathy</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Myelopathy</td>
</tr>
<tr>
<td>Seizure disorder</td>
</tr>
</tbody>
</table>

with embolic phenomena in the setting of antiphospholipid antibody syndrome. One particularly challenging diagnostic dilemma is distinguishing steroid psychosis from acute psychotic symptoms caused by CNS lupus, a situation with a very different treatment approach. Soliciting help from psychiatric and rheumatologic colleagues is appropriate in any patient thought to have CNS lupus.

Sarcoidosis

Sarcoidosis can present with a large variety of both systemic and neuropsychiatric symptoms. It is estimated that 5% to 15% of patients with sarcoidosis develop related neurologic symptoms.\textsuperscript{39,40} However, sarcoidosis is rare, with an estimated incidence of 10 to 40 new cases per 100,000 patients per year,\textsuperscript{41} making neurosarcoidosis rarer still. Sarcoidosis can affect both the central and peripheral nervous systems, and most frequently causes cranial neuropathies.\textsuperscript{42} Neurosarcoidosis can cause nearly any neurologic symptom, including aseptic meningitis, seizures, peripheral neuropathies, psychiatric symptoms, and small fiber neuropathies causing symptoms such as pain, restless legs, and autonomic neuropathies.\textsuperscript{43} Hypothalamic inflammation can cause a variety of symptoms including polyuria (caused by central diabetes insipidus or primary polydipsia) and changes in sleep, appetite, and temperature regulation.\textsuperscript{44} The diagnosis of neurosarcoidosis is made based on history, radiologic and laboratory evaluation, and histology showing granulomatous disease. Useful diagnostic tests include images of the CNS and chest (to detect the presence of hilar adenopathy), serum angiotensin-converting enzyme (ACE) levels (which are neither specific nor sensitive and can be increased in a variety of systemic diseases), and CSF evaluation in the setting of CNS symptoms.\textsuperscript{42} CSF findings suggesting neurosarcoidosis include pleocytosis, increased protein, and low glucose, although these levels are normal in about one-third of patients with neurosarcoidosis.\textsuperscript{45} CSF ACE levels are also nonspecific but can be useful in monitoring response to therapy.

Neurosarcoidosis carries an uncertain prognosis, mainly because of its low incidence and the absence of long-term follow-up studies. Treatment recommendations similarly are based on expert opinion and clinical experience rather than data from randomized controlled trials. Treatment of neurosarcoidosis includes systemic steroids and cytotoxic immunosuppressants, as are used in treatment of sarcoidosis elsewhere in the body. The efficacy of tumor necrosis factor alpha blockers has also been shown in certain refractory cases.\textsuperscript{46}

ENDOCRINOLOGIC

Thyroid Disorders

Both hypothyroidism and hyperthyroidism can cause neuropsychiatric symptoms. This article focuses on neurologic manifestations in adult-onset, rather than congenital, hypothyroidism. Hypothyroidism can cause cognitive impairment and symptoms of depression, usually co-occurring with other systemic symptoms of hypothyroidism including fatigue, cold intolerance, dry skin, weight gain, and lethargy.\textsuperscript{47} In addition, hypothyroidism caused by autoimmune thyroiditis (Hashimoto disease) is associated with encephalopathy, although this is thought to be mediated by an immunologic process rather than by low levels of circulating thyroid hormone. Cognitive impairment in the setting of hypothyroidism has an unknown mechanism, although some investigators have postulated that anxiety and depression, both highly prevalent, may be impairing memory and concentration, as they can in euthyroid patients.\textsuperscript{48} Screening for hypothyroidism in patients with newly diagnosed cognitive impairment is widespread, because this is considered to be a reversible form of impairment. However,
the yield of such screening is low, and the evidence for reversibility of cognitive symptoms with thyroid supplementation is mixed, with the possibility of incomplete recovery, particularly in the case of subclinical hypothyroidism and in the presence of other common comorbid conditions such as Alzheimer disease. Hypothyroidism is also associated with other neurologic symptoms and syndromes including ataxia, peripheral neuropathies (including carpal tunnel syndrome and symmetric polyneuropathies), and myopathies, which present with proximal muscle weakness and pain. Most of these syndromes respond to thyroid replacement.

Hyperthyroidism can also cause both CNS and peripheral nervous system syndromes. CNS manifestations can include psychiatric symptoms such as irritability and anxiety, and, in the elderly, depression and lethargy. In addition, patients can present with cognitive deficits, include memory impairment, inattention, and decreased productivity. Other CNS symptoms of hyperthyroidism include tremor and seizures, and, rarely, stroke and chorea. Peripheral nervous system manifestations can include peripheral neuropathies (classically a symmetric distal sensory polyneuropathy), myasthenia gravis, hypokalemic periodic paralysis, and myopathy. Diagnosis of these various syndromes is made using serum measurement of thyroid function, as well as possible additional testing for each specific symptom constellation (not discussed in this article). Many of these syndromes respond to treatment and either resolve or improve with restoration of euthyroidism.

**Cushing Syndrome**

Hypercortisolism (Cushing syndrome) causes neuropsychiatric symptoms in more than half of affected patients. Common psychiatric symptoms include dysphoria, irritability, appetite changes, anxiety and panic attacks, mania, psychosis, and insomnia. Excess cortisol can also have profound effects on cognitive function, with memory impairment being the most common manifestation. Attention, reasoning, comprehension, and information processing can also be affected. Neuropsychiatric and other symptoms of hypercortisolism are nonspecific, and diagnosis is made by measuring salivary or urinary cortisol levels, and by administration of the dexamethasone suppression test. The specific cause of Cushing syndrome is established by ruling out exogenous administration of glucocorticoids, then by localizing the defect along the hypothalamic-pituitary-adrenal axis. Thus, subsequent measurement of serum adrenocorticotropic hormone (ACTH) is performed, followed by further laboratory testing and imaging of the pituitary or adrenal glands, if indicated. Treatment varies depending on the underlying cause. Related neuropsychiatric symptoms typically improve with treatment, but often do not fully resolve, and patients with a history of treated Cushing syndrome are commonly left with residual psychiatric symptoms and cognitive impairment.

**Adrenal Insufficiency, Including Primary Adrenal Insufficiency (Addison Disease)**

Adrenal insufficiency, which can include deficiencies in glucocorticoids, aldosterone, and androgens, can also cause nonspecific systemic symptoms that overlap with psychiatric symptoms, most commonly fatigue, lassitude, generalized weakness, and loss of appetite. In addition, patients with chronic adrenal insufficiency can have neuropsychiatric symptoms including cognitive impairment, depression, and psychosis. Diagnosis is made from serum ACTH and cortisol levels, and subsequent laboratory evaluation (metyrapone testing, corticotropin-releasing hormone stimulation testing) as indicated. After hypocortisolism has been established, ACTH levels are used to determine whether the cause is central or peripheral, and then the underlying cause is sought. Treatment with replacement of glucocorticoids, mineralocorticoids, and
androgens is complex and depends on the clinical scenario and context. As with many of the other medical conditions described earlier, patients who are treated may not have complete resolution of neuropsychiatric symptoms or subjective health status.67

METABOLIC
Vitamin Deficiencies

Vitamin deficiencies can also cause neuropsychiatric symptoms, particularly thiamine (vitamin B1) and cobalamin (B12) deficiencies. Thiamine deficiency classically causes Wernicke-Korsakoff syndrome, which can be further subdivided into 2 distinct clinical entities: Wernicke encephalopathy (WE) and Korsakoff syndrome. WE is an acute syndrome characterized by cognitive impairment, ataxia, and oculomotor dysfunction, with most patients having some, but not all, of the classic symptom triad.68 The cognitive impairment of WE typically includes inattention and disorientation. Korsakoff syndrome is a chronic condition characterized primarily by anterograde and retrograde memory impairment with conservation of long-term memory. Both syndromes are most commonly associated with excessive alcohol use and inadequate nutrition. Diagnosis is made by documentation of serum thiamine deficiency with a compatible clinical presentation. Imaging of the CNS can help suggest the diagnosis and rule out alternative causes. Although WE is treatable, significant deficits may persist even after adequate thiamine repletion.68 Patients with Korsakoff syndrome typically respond poorly to treatment and require long-term supportive care.

Cobalamin (vitamin B12) deficiency is usually caused by impaired absorption in the setting of pernicious anemia or gastric/small bowel disorders. Cobalamin deficiency can cause a wide range of neuropsychiatric symptoms, including mood disorders; psychosis; cognitive impairment; and disorders of the sensory, motor, and autonomic nervous systems (Table 3 provides a list of possible neuropsychiatric symptoms).69 These neuropsychiatric complications can occur in the absence of any hematologic evidence of megaloblastic anemia or other conditions associated with B12 deficiency. These symptoms can occur early or later in the course of B12 deficiency as well and their severity is inversely related to the severity of megaloblastic anemia.70 Neurologic symptoms of cobalamin deficiency typically respond to treatment within the first 3 months, with nearly half of patients experiencing full recovery. Extent of recovery is related to the disease severity and duration of symptoms.71

<table>
<thead>
<tr>
<th>Psychiatric</th>
<th>Neurologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Sensory polyneuropathy</td>
</tr>
<tr>
<td>Anxiety/panic disorder</td>
<td>• Impaired vibration sense</td>
</tr>
<tr>
<td>Psychosis</td>
<td>• Impaired proprioception</td>
</tr>
<tr>
<td>Mania</td>
<td>Decreased visual acuity</td>
</tr>
<tr>
<td>Hallucinations/delusions</td>
<td>Dysgeusia/dysosmia</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Urinary/fecal incontinence</td>
</tr>
<tr>
<td></td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td></td>
<td>Cerebellar ataxia</td>
</tr>
<tr>
<td></td>
<td>Cognitive impairment</td>
</tr>
<tr>
<td></td>
<td>• Memory impairment</td>
</tr>
<tr>
<td></td>
<td>• Disorientation</td>
</tr>
<tr>
<td></td>
<td>Obtundation</td>
</tr>
<tr>
<td></td>
<td>Spasticity</td>
</tr>
</tbody>
</table>

Calcium Disorders

Both hypocalcemia and hypercalcemia can cause neuropsychiatric manifestations. The severity of symptoms caused by hypocalcemia depends on both the acuity of change in calcium levels and the degree of hypocalcemia. Hypocalcemia can cause seizures and increased neuromuscular excitability, as well as psychiatric symptoms such as emotional lability, depression, psychosis, and anxiety. Hypercalcemia can cause confusion, lethargy, generalized weakness, and in severe cases coma and death. These symptoms typically resolve with correction of the underlying electrolyte abnormality.

Porphyrias

Acute porphyrias, rare disorders that result from abnormalities in heme biosynthesis, can cause neurologic and psychiatric symptoms. The porphyrias that can cause neurologic sequelae include the acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria, and variegate porphyria. AIP is the most common of these rare, autosomal dominant disorders with incomplete penetrance, and all three can manifest similar neuropsychiatric sequelae. These acute porphyrias typically present with neurovisceral symptoms: the classic triad consists of abdominal pain, peripheral neuropathy, and altered mental status. There are isolated reports of patients presenting with neuropathy, encephalopathy, or psychosis, without associated abdominal symptoms. The peripheral neuropathy seen with the porphyrias is usually a motor neuropathy, preferentially affecting proximal muscles. Sensory neuropathies are also common, and can follow either a stocking-glove or more central pattern of distribution. Cranial neuropathies are also a common manifestation of acute attacks. Psychiatric symptoms are present in more than half of patients with symptomatic acute porphyria. These psychiatric sequelae commonly include psychotic disorders, but can also include depression, anxiety, and delirium. Diagnosis is made by qualitative testing for urine porphobilinogen (PBG) during an acute attack with additional second-line tests including quantitative PBG, plasma, erythrocyte, and fecal porphyrins, and enzymatic and DNA testing to confirm the diagnosis. Prevention of acute attacks is an important aspect of long-term management and may include careful attention to diet, avoidance of medications known to exacerbate acute porphoria, and heme arginate (hemin) prophylaxis. Treatment of acute attacks typically involves symptom-directed therapies and supportive care, as well as IV hemin, and dietary loading with carbohydrates. Patients often require hospitalization for acute attacks.

Wilson Disease

Wilson disease is a rare, autosomal recessive disorder of copper transport. In addition to liver failure, which is the best known manifestation of this disease, patients can also have neurologic sequelae. The prevalence estimates of neurologic symptoms attributable to Wilson disease are widely variable. Neurologic sequelae can include choreoathetosis, dysarthria, dystonia, tremor, ataxia, parkinsonism, and cognitive impairment, usually involving either the frontal lobe or a subcortical dementia. Although serum ceruloplasmin is a commonly used screening test, 24-hour urine copper quantification is more sensitive. Most patients with neurologic manifestations of Wilson disease also have Kayser-Fleischer rings present on slit-lamp ophthalmologic examination. Wilson disease is unusual compared with some of the other medical conditions discussed here, in that early diagnosis and treatment can prevent severe neurologic symptoms and appropriately treated patients can even have a normal life span.
NEOPLASTIC

Paraneoplastic Syndromes

Paraneoplastic syndromes involve organ and tissue damage distant from the site of a malignancy or metastases, are thought to be autoimmune mediated, are associated with antineuronal antibodies, and may affect the peripheral nervous system or CNS. They may affect any anatomic part of the nervous system, and any specific cell type as well, making the symptoms and signs potentially attributable to paraneoplastic disease numerous. Paraneoplastic syndromes can be seen in patients with already diagnosed neoplasms, but can sometimes precede the diagnosis of cancer, making awareness of this condition important for clinicians. Symptoms can range from peripheral neuropathies to neuropsychiatric symptoms including cognitive impairment, mood disorders, and changes in consciousness. See Table 4 for a listing of possible neurologic and psychiatric abnormalities associated with paraneoplastic syndromes.

Limbic encephalitis is one of the best described neuropsychiatric manifestations of paraneoplastic syndromes. It can be caused not only by paraneoplastic processes but also autoimmune diseases outside the setting of cancer and viral infections. Limbic encephalitis involves gray matter in the limbic area of the brain (amygdala, cingulate gyrus, and hippocampus) and patients typically present with short-term memory loss, seizures, and psychiatric symptoms ranging from mood disorders (depression, irritability) and personality changes to hallucinations. Treatment is directed at treatment of the underlying cancer, and immune suppression, although there are no established protocols or guidelines for treating paraneoplastic syndromes.

FUTURE CONSIDERATIONS/SUMMARY

Early recognition of medical conditions underlying neuropsychiatric symptoms is critical for effective management, particularly for those patients with other signs or symptoms.
symptoms that might suggest a non-neuropsychiatric origin of the illness and/or systemic cause. The number of medical conditions that have been associated with such symptoms is vast; thus, casting a broad differential diagnosis is imperative when such unexplained, and often acute, symptoms are present. Treatment of the underlying condition causing these symptoms is usually indicated, as is careful attention to symptom management. Certain conditions are well understood and treatments well established, such as the electrolyte abnormalities listed earlier, although knowledge of many of these complex causes continues to evolve, as does understanding of the best therapeutic interventions, particularly given that many of these diseases are rare. Through careful history taking, physical examination, and ancillary testing when indicated, these medical conditions can rapidly be identified and treated, usually resulting in symptom improvement, if not complete resolution.

REFERENCES


