HHS Public Access

Author manuscript

Crit Care Clin. Author manuscript; available in PMC 2018 January 17.

Published in final edited form as:

Crit Care Clin. 2017 July ; 33(3): 681–712. doi:10.1016/j.ccc.2017.03.007.

Neuropsychiatric Aspects of Infectious Diseases:

An Update

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Keywords

Neuropsychiatric disturbances; Infectious diseases; Delirium; HIV-AIDS; Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; Herpes simplex encephalitis; Neurocysticercosis; Neurosyphilis; Creutzfeldt-Jakob disease; Neuroborreliosis

INTRODUCTION

Among the critically ill, infectious diseases can play a significant role in the etiology of neuropsychiatric disturbances. All critical care physicians are familiar with delirium as a secondary complication of systemic infection. This article focuses on key infectious diseases that commonly and directly produce neuropsychiatric symptoms, including direct infection of the central nervous system (CNS), human immunodeficiency virus (HIV) infection, and AIDS.

HIV-AIDS is often seen as the modern "great imitator," a complex infectious disease with multiple manifestations and interplay of myriad biopsychosocial factors, including neuropsychiatric disorders related to direct HIV-1 brain invasion, CNS opportunistic infections, manifestations of concurrent drug abuse, hepatitis C coinfection, and iatrogenic complications. Differential diagnosis and management of HIV-AIDS–related neuropsychiatric disturbances can serve as a paradigm for other infectious diseases that have neuropsychiatric manifestations.

MEDICAL HOSPITALIZATION IN HUMAN IMMUNODEFICIENCY VIRUS–AIDS

With the widespread availability of highly active antiretroviral therapy (HAART) for HIV infection in developed countries, there have been dramatic declines in HIV-related hospital admissions. Between 1995 and 1997, admissions dropped 33% to 75%.[1–4] Since that time,

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rates have stabilized or rebounded slightly. The reasons for medical hospital admission have also shifted. In 2 urban hospital studies,[3, 4] a drop in hospitalization caused by opportunistic infections and cancers was observed, contrasting with a rise in nonopportunistic complications, such as hepatitis C and cardiovascular disease. Mean CD4 counts of HIV inpatients were seen to increase by more than 100 cells/mm^3 from 1995 to 2001.[3] During 1990 to 2011, among persons with AIDS, the annual rate of death due to HIV-attributable causes has also decreased by 89%.[5]

Factors that seem to confer risk for medical hospitalization in the HAART era include low CD4 count, female gender, lack of antiretroviral treatment, and injection drug use.[3, 4] The sociodemographic characteristics of those at risk reflect the shifting demographics of the HIV epidemic, limitations in access to care, and poor adherence to antiretroviral treatment.

EPIDEMIOLOGY OF PSYCHIATRIC DISORDERS IN MEDICAL INPATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS–AIDS

There are extensive epidemiologic data regarding psychiatric disorders in ambulatory patients with HIV-AIDS. Overall, studies reveal high rates of lifetime and current substance abuse and depressive and anxiety disorders (see Ferrando and Tiamson[6] for a review of this literature). As seen in Table 1, among medially hospitalized patients with HIV, studies indicate a similar profile; however, delirium, dementia, and manic-spectrum disorders seem to be more common.[7–11] The most frequently diagnosed disorders are in the depressive spectrum (range, 27%–83%), including depression secondary to medical condition (or organic mood disorder), adjustment disorder with depressed mood, major depressive disorder, or dysthymic disorder. Delirium is diagnosed in 8% to 29% of patients, regardless of HIV stage, and is often reported to be concurrent with HIV-associated dementia, diagnosed in 8% to 22% of cases. Substance use disorders are diagnosed in 11% to 36% of inpatients with AIDS and up to 63% in patients who are HIV-positive without AIDS. One study found that bipolar disorder and HIV-associated mania occurred in 11% of medical inpatients.[11]

HUMAN IMMUNODEFICIENCY VIRUS AND THE BRAIN

Since the beginning of the HIV epidemic, it has been recognized that HIV can infect the CNS and produce a range of cognitive and behavioral symptoms that become more frequent and severe as the immune system declines and symptomatic illness and AIDS ensue. In 1991, the American Academy of Neurology published research diagnostic criteria for HIV-associated cognitive, motor, and behavior disorders,[12] which remained in widespread use until the diagnostic criteria were recently updated by a work group convened at the National Institute of Mental Health.[13] Based on cumulative research and clinical evidence, this group described 3 HIV-associated neurocognitive disorders (HANDs): (1) asymptomatic neurocognitive impairment, (2) mild neurocognitive disorder, and (3) HIV-associated dementia. The asymptomatic neurocognitive impairment category recognizes that a substantial percentage of patients who infected with HIV have demonstrable impairment on neuropsychologic testing but little or no perceptible functional impairment. The latter 2 disorders (mild neurocognitive disorder and HIV-associated dementia) present with

cognitive and behavioral symptoms associated with functional impairment (mild in mild neurocognitive disorder, moderate to severe in HIV-associated dementia). HANDs have been found to predict shorter survival,[14, 15] especially in the setting of virologic failure on HAART.[16] The cognitive symptoms of HANDs are characteristic of subcortical-frontal pathology and include impairment in psychomotor processing speed, executive function, and verbal memory. The potential behavioral manifestations are broad and include apathy, depression, anxiety, mania, and psychosis.

Neuropathologically, HIV traverses the blood-brain barrier primarily by infected blood mononuclear cells, becoming activated macrophages once they enter the brain. Onset of neural injury may date to initial viral invasion and the transient early period of unchecked viremia and marked immunosuppression of the seroconversion period.[17] Neuropathologic changes seem to be a result of CNS immune activation with release of neurotoxic cytokines and metabolites. Substance abuse is an important cofactor for HIV neuropathology.[18] Subcortical brain structures, such as the basal ganglia and periventricular white matter, are most affected. If unchecked, this immune cascade leads to neuronal cell apoptosis. Effective suppression of CNS viral replication and the resulting immune activation has the potential, however, to reverse at least some of the neuropathologic changes.

HIV-associated neuropathology has received heightened attention in recent years because of 2 associated developments. First, HIV-1 viral load monitoring has demonstrated that the CNS is an independent sanctuary site of viral replication.[19] The level and genetic profile of HIV in the peripheral circulation may not correlate with that in the CNS. The second development relates to the recognition that antiretroviral medications have differing levels of penetration into the CNS. It is hypothesized that poorly penetrating antiretrovirals might inadequately treat CNS infection despite being effective peripherally. This has led to concerns that actively replicating virus in the CNS could cause progressive cognitive decline in otherwise healthy HIV-positive individuals and could also lead to a reseeding of the virus into the peripheral circulation. Indeed, better CNS antiretroviral penetrance has been found to correlate with better suppression of HIV in the cerebrospinal fluid (CSF).[20] However, this approach is controversial, as higher CSF Penetration Effectiveness scores correlate with lower HIV RNA load in the CSF but do not necessarily correlate with better cognition.[21] HAND is common in patients with HIV on combination treatment with a reported frequency of 25% to 47%.[22] There has been a reduction in the incidence of HIV-associated dementia from 7% per year in the pre-HAART era to approximately 2% to 3%.[23] However, cases still occur in patients with HIV who are untreated, inadequately treated, or in persons who have “CNS escape” (a phenomenon in which antiretroviral therapy [ART] controls HIV in the periphery but not in the CNS).[24] HAART regimens have been shown to reduce CSF viral load to undetectable levels,[19] to reverse white matter lesions on MRI,[25] to reverse brain metabolic abnormalities detected by proton magnetic resonance spectroscopy,[26] and also to improve neuropsychologic test performance.[27–29] Despite these hopeful findings, however, functionally significant cognitive and behavioral disturbances, without frank dementia, may persist in approximately one-fourth of patients treated with HAART,[30, 31] impeding adherence to treatment[32] and ability to work.[33]

DIFFERENTIAL DIAGNOSIS

Differential diagnosis is paramount when investigating for medical and neuropsychiatric etiologic factors related to HIV illness and its treatment (Box 1).

First, in assessing the hospitalized patient with HIV-AIDS, it is important to query for personal and family psychiatric history because neuropsychiatric complications may be a manifestation of preexisting psychopathology.[34, 35] Even in the presence of a prior psychiatric history, however, it is imperative to rule out potentially exacerbating, if not etiologic, medical factors. HANDs are associated with a range of cognitive or behavioral symptoms, including apathy, depression, sleep disturbances, mania, and psychosis. CNS opportunistic illnesses and cancers also can present with a wide range of neuropsychiatric symptoms as a result of both focal and generalized neuropathologic processes (Table 2).

Substance intoxication and withdrawal also are common in the medical inpatient setting. HIV-infected substance users have high rates of preexisting comorbid psychopathology that may be exacerbated by ongoing substance use. Further, abuse of multiple substances concurrently (eg, opioids, cocaine, benzodiazepines, alcohol) can result in complex intoxication and withdrawal states that may be very difficult to treat.

Hepatitis C coinfection is associated with multiple neuropsychiatric complaints, most frequently fatigue, depression, and cognitive dysfunction. The pattern of cognitive impairment is similar to that of HIV, with impairment in attention, concentration, psychomotor processing speed, verbal memory, and executive dysfunction. Patients with end-stage liver disease and cirrhosis experience superimposed delirium (hepatic encephalopathy). Combination pegylated interferon alpha-2a treatment for hepatitis C has been extensively documented to cause neuropsychiatric side effects, including depression, suicidal ideation, anxiety, sleep disturbance, fatigue, mania, psychosis, delirium, and cognitive dysfunction.[36]

Multiple antiretroviral and other medications used in the context of HIV have been reported to have neuropsychiatric side effects. These include zidovudine, didanosine, abacavir, nevirapine, efavirenz, and interferon alpha-2a.[37] Most of these are uncommon or rare and causal relationships are often difficult to determine. The most widespread clinical concern has been generated by reports of sudden-onset depression and suicidal ideation associated with interferon alpha-2a and efavirenz. Early reports suggested that efavirenz may be associated with at least transient neuropsychiatric side effects in excess of 50% of patients.[38] Reported effects are protean and include depression, suicidal ideation, vivid nightmares, anxiety, insomnia, psychosis, cognitive dysfunction, and antisocial behavior. Drug interactions between antiretroviral and psychotropic medications are important aspects of differential diagnosis in the hospital setting. In one study, HIV-AIDS medical inpatients were prescribed an average of 7 medications during their admission.[11] Factors influencing drug-drug interactions include medical illness severity, prior substance abuse, the likelihood of multiple medications being initiated simultaneously, changes in volume of distribution and protein binding, and hepatic and renal impairment.

Inpatients with HIV-AIDS often experience endocrinologic derangements that may produce behavioral symptoms. These include clinical and subclinical hypothyroidism, [39] hypogonadism,[40] adrenal insufficiency,[41] and Graves disease (autoimmune thyroiditis).[39] Thyroid deficiency, including its subclinical forms, is present in approximately 36% of HIV-infected patients.[39] Testosterone deficiency, with clinical symptoms of hypogonadism, is present in up to 50% of men with symptomatic HIV or AIDS and is likely to be present with concurrent acute medical illness.[40] Deficiency of adrenal glucocorticoid production is present in up to 50% of severely ill patients with HIV.[41] These endocrine deficiency states have been associated with fatigue, low mood, low libido, and loss of lean body mass and may be ameliorated by correction of the deficiency. Graves disease presents in the acute stages with activation symptoms including anxiety, irritability, insomnia, weight loss, mania, and agitation.

DIAGNOSTIC EVALUATION

The psychiatric evaluation of the inpatient with HIV-AIDS is consistent with the broad differential diagnosis and is focused on identifying potentially reversible underlying etiologies. A thorough psychiatric evaluation, including presenting symptoms, personal and family history of psychiatric illness and substance abuse, and a cognitive functioning examination are essential. Box 2 contains a listing of such diagnostic tests.

In general, the diagnostic workup should include complete blood count with differential, serum chemistries (including liver and renal function tests, fasting glucose, and creatine phosphokinase), chest radiograph, electrocardiogram, blood and urine cultures (if indicated), toxicology screen, and psychotropic medication serum levels (when available). Depending on the clinical presentation, assays of thyroid function; vitamins B6 and B12; Venereal Disease Research Laboratory; serum total, free, or bioavailable testosterone; adrenocorticotropic hormone stimulation; and 24-hour urinary cortisol may be obtained. If brain imaging is required, MRI of the brain with gadolinium contrast is preferred over computed tomography (CT) because it produces better visualization of brain tissue and of subcortical and posterior fossa structures and focal lesions. A lumbar puncture also may be obtained if necessary under sedation with fluoroscopic guidance. Results are often nonspecific, but important studies include opening pressure; culture (viral, fungal, mycobacterial); cell count; protein; neopterin; b2-microglobulin; and polymerase chain reaction testing for cytomegalovirus, Epstein-Barr virus, John Cunningham (JC) virus, herpes simplex virus (HSV), and HIV-1.

PSYCHIATRIC DISORDERS IN HUMAN IMMUNODEFICIENCY VIRUS–AIDS AND THEIR TREATMENT

Depression

Depression is the most common psychiatric symptom and diagnosis among medical inpatients with HIV-AIDS. Symptoms are often attributed to adjustment disorder or to medically related (organic) factors that may be transient, related to improvement in physical symptoms. Major depressive disorder (MDD) may be a reaction to an HIV diagnosis,

medical illness, HIV stigma, or the direct CNS effects of HIV as mediated by altered cytokine and neurotransmitter metabolism.[42] Identifying and treating MDD is important to long-term management because prolonged MDD is associated with decreased adherence to ART.[43, 44] In one prospective study assessing depressive symptoms at admission and discharge, however, 28% of medical inpatients with HIVAIDS had severe depression that persisted at discharge.[45] In another study, 76% of patients who had a depressive disorder during their admission continued to have significant depressive symptoms 3 to 6 weeks after discharge, with significant predictors of depression during and after medical hospitalization including being a woman, having an AIDS diagnosis, and having poor social support.[11]

In the medical inpatient setting in particular, the diagnosis of depressive disorder in HIV-infected patients may be confounded by somatic symptoms common to depression, HIV illness, and its complications. HIV infection stimulates rising levels of proinflammatory cytokines, such as interleukin-6, interleukin-1 beta, tumor necrosis factor-alpha and interferon-gamma, that are associated with “sickness behavior” (fever, hypersomnia, anorexia, decreased motor activity, and loss of interest in the environment).[46] These include fatigue, appetite loss, sleep disturbance, and cognitive disturbances. Generally, in the presence of persistent depressed mood or loss of interest, an inclusive approach toward somatic symptoms is preferred. This is because affective and somatic subscales of depression screening instruments (eg, the Beck Depression Inventory) are highly intercorrelated, that these symptoms are more closely linked to measures of depression than to measures of HIV disease severity, and that both affective and somatic symptoms improve with antidepressant treatment.[47, 48] However, persons with HIV may be screened using the Beck Depression Inventory for Primary Care, a tool that focuses on nonphysical symptoms as well.[49]

In the medical inpatient setting, when antidepressant medication treatment is considered, particular attention must be paid to side-effect profile, hepatic and renal function, and the potential for drug interactions. In addition to standard antidepressants, such as serotonin and serotonin-norepinephrine reuptake inhibitors, the initiation of psychostimulants and anabolic steroids, particularly testosterone, is frequently used in the inpatient setting and is given particular attention here.

Psychostimulants have been studied for the treatment of depressed mood, fatigue, and cognitive impairment in the context of HIV infection, particularly in advanced illness and where rapid onset of action is desirable. Agents studied include methylphenidate (5–90 mg/d), dextroamphetamine (5–20 mg/d), pemoline (35–150 mg/d), and the wakefulness agent modafinil (50–200 mg/d).[50–53] These agents are efficacious in treating depressive symptoms in patients with advanced HIV. The primary side effect is overstimulation.

Testosterone deficiency, with clinical symptoms of hypogonadism (depressed mood, fatigue, diminished libido, decreased appetite, and loss of lean body mass) is present in up to 50% of men and women with symptomatic HIV or AIDS.[40] The most common screening test for testosterone deficiency is total serum testosterone (deficiency is defined as <300–400 ng/dL in men); however, serum-free (deficiency: <5–7 pg/mL in men; <3 pg/mL in women) and bioavailable testosterone may be more accurate measures. For testosterone replacement in

men, commonly used testosterone preparations include esterified depot testosterone (propionate, enanthate, cypionate, initiated at 100–200 mg intramuscularly every 2 weeks, maximum 400 mg intramuscularly weekly), transdermal skin patches (1 to 2 patches, 5–10 mg, to clean, dry skin daily), and transdermal testosterone gel (1 to 4 packets, 25–100 mg, to clean, dry skin daily), with the depot preparations being the least expensive and most studied. Patch and gel formulations may produce less variability in serum testosterone levels and in target symptoms. In women, transdermal testosterone, 150 mg per day or equivalent, may be used to improve energy, well-being, muscle mass, and restore normal menstrual functioning.[40] Reported side effects for men include irritability, tension, reduced energy, hair loss, testicular atrophy, reduced ejaculate volume, and acne. For women, there is particular concern for virilizing side effects; however, clinically these have been minimal in the setting of physiologic replacement dosing in the range described.

Delirium

The most common neuropsychiatric complication in hospitalized patients with AIDS is delirium.[54] Delirium is diagnosed in 11% to 29% of hospitalized patients with HIV-AIDS. [11] There are no data regarding specific or distinguishing symptom characteristics for the delirium seen in patients with HIV. Both the hypoactive and hyperactive variants of delirium are seen, and in addition to cognitive disturbance, symptom manifestations include apathy, dysphoria, agitation, fearfulness, delusions, and hallucinations.[55]

Delirium in the patient with HIV-AIDS is often superimposed on HANDs, particularly dementia, and patients with these disorders are at increased risk for the development of delirium when medically hospitalized. The etiology of delirium in patients with HIVAIDS is generally multifactorial. Breitbart and colleagues[55] reported a mean of 12.6 medical complications in 30 delirious patients with AIDS, with the most common being hematologic (anemia, leukopenia, thrombocytopenia, hypoalbuminemia) and infectious diseases (eg, septicemia, systemic fungal infections, *Pneumocystis carinii* pneumonia, tuberculosis, and disseminated viral infections). Other potential etiologies were discussed previously in the differential diagnosis section.

Central to the treatment of delirium is treatment of its underlying medical causes. Symptomatic treatment includes educational, environmental, and psychopharmacologic interventions. Education regarding the risk and nature of delirium delivered to patients, their families, and the treatment team can be preventive and can result in earlier treatment and improved outcomes. Environmental interventions include titrating the level of stimulation, sitting the patient up, placing patients next to a window, frequent orientation, stabilizing sleep-wake cycles, and placing familiar people and orienting objects in the room.

In terms of pharmacologic treatment, most practitioners treat delirium with atypical antipsychotics, including olanzapine (available with dissolving oral preparation and intramuscularly), risperidone (available in dissolving oral preparation), quetiapine, aripiprazole (available intramuscularly), and ziprasidone (available intramuscularly). The only double-blind clinical trial of delirium treatment in AIDS, however, compared haloperidol, chlorpromazine, and lorazepam.[55] In that study, Breitbart and colleagues[55] screened medical inpatients with HIV for delirium. Treatment was initiated early, and when

symptoms were mild to moderate in degree. Patients were severely medically ill, because 9 (30%) of the 30 patients died within 1 week after completing the protocol. There were 3 important findings. First, haloperidol (mean dose, 2.8 mg/d acutely and 1.4 mg/d maintenance) and chlorpromazine (mean dose, 50 mg/d acutely and 36 mg/d maintenance) were equally efficacious. Second, the lorazepam arm (mean dose, 3 mg acutely) was stopped early because of worsening of delirium symptoms, including oversedation, disinhibition, ataxia, and increased confusion. Third, adverse effects in the antipsychotic arms were limited and included mild extrapyramidal symptoms (EPS), such as decreased expressiveness, rigidity, tremor, and mild akathisia. Open-label studies and case reports suggest that the atypical antipsychotics clozapine, risperidone, and ziprasidone benefit patients with AIDS with psychosis and/or delirium.[56]

Delirium is common in hospitalized patients with HIV-AIDS, who should be assessed frequently for early detection and treatment. A combination of psychoeducational, environmental, and pharmacologic interventions, primarily with neuroleptic medications, is recommended. Benzodiazepines should be avoided, except in cases of severe agitation that fails to respond to antipsychotic agents or patients experiencing delirium secondary to alcohol or other CNS-depressant agent withdrawal, and patients should be monitored closely for the emergence of EPS. There is a higher susceptibility of patients with HIV to EPS, even with exposure to drugs with low potential for inducing EPS.[57] Extreme sensitivity to EPS is encountered in patients with HIV-dementia.[58] Marked neuronal degeneration in the basal ganglia of patients with HIV may contribute to these findings because of the accompanying dopaminergic neuron destruction and/or alteration.[59]

Mania

Manic symptomatology has been reported in 11% of all medically hospitalized patients with HIV-AIDS[11] and may be seen in conjunction with primary bipolar illness or with CNS HIV infection (HIV-associated mania). Descriptively, HIV-associated mania is found to be a late-onset, secondary affective illness associated with HIV infection of the brain, being less associated with a personal or family history of mood disorder. In addition, the symptomatology of HIV-associated mania may include more irritability, less hypertalkativeness, and more psychomotor slowing and cognitive impairment compared with primary bipolar mania.[60] Given that HIV-associated mania is directly related to HIV brain infection, antiretroviral agents that penetrate the blood-brain barrier may offer some protection from incident mania.[61] The mechanisms are poorly understood; however, the HIV nef protein is reported to alter CNS dopamine metabolism leading to hyperactive, “maniclike” behaviors in animal models.[62]

The choice of psychotropic drugs to treat HIV mania is based on case reports, and open-label studies, rather than randomized controlled trials, as well as the desire to avoid adverse drug interactions, and the avoidance of HIV-specific side effects. HIV mania may improve with an approach that combines resolution of the underlying CNS process, use of a mood-stabilizing drug, and/or addition of an antipsychotic drug.[63] Valproic acid is metabolized in the liver, and liver disease is common in HIV-positive persons; further, valproic acid has interactions with many ART drugs.[64, 65] This must be weighed against the potential

disadvantages of other mood stabilizers, such as lithium, which can exacerbate renal disease, or carbamazepine, which can induce bone marrow suppression, hepatotoxicity, and induce the metabolism of ART (particularly protease inhibitors).[64, 66] Lamotrigine has been tested for HIV-associated peripheral neuropathy and may be useful for treating mixed mania or bipolar depression in HIV; however, patients with overt manic symptomatology generally require a traditional mood stabilizer. This anticonvulsant requires careful upward dose titration because of risk of severe hypersensitivity (Stevens-Johnson syndrome).

Given the limitations of mood stabilizers in HIV, there is widespread clinical use of atypical antipsychotics for acute and maintenance treatment of HIV-associated mania; however, there are no clinical trial data. Clinicians generally choose olanzapine, risperidone, ziprasidone, or quetiapine as alternatives to traditional mood stabilizers[58, 67]; however, these agents may exacerbate metabolic syndrome or cause EPS in patients with extensive basal ganglia HIV involvement. Benzodiazepines may be useful for adjunctive treatment, but acute and maintenance therapy may be complicated by tolerance, dependence, and cognitive impairment, including the possibility of causing delirium and disinhibition.

Psychosis

HIV infection may be directly linked to the onset of psychosis, which is defined by the presence of thought disorder, hallucinations, or delusions. Psychosis in HIV is most often a manifestation of substance intoxication or withdrawal, delirium, HANDs, mood disorders with psychotic features, or schizophrenia. Estimates of the prevalence of new-onset psychosis in patients with HIV range from 0.5% to 15.0%.[68] One study compared 20 HIV-infected patients with new-onset psychosis (and no prior psychotic episodes or current substance abuse) with 20 nonpsychotic patients matched for demographics and HIV illness. The former group tended to have worse global neuropsychologic impairment, was more likely to have a prior history of substance abuse, and had significantly higher mortality at follow-up, suggesting that psychotic patients with HIV-AIDS had an increased CNS vulnerability.[69]

Persons with HIV-associated secondary psychosis are reported to show more disorders of consciousness, orientation, attention, and memory than patients with primary serious mental illness.[70] They also tend to report less bizarre delusions, have a more variable course, and are more likely to have eventual remission of their psychosis.[71]

Patients infected with HIV with primary psychotic disorders, such as schizophrenia and schizoaffective disorder, may have poor access to HIV care, may present to the emergency and medical inpatient setting with untreated advanced HIV illness, and may be at risk for poor adherence to care, unless provided with comprehensive supportive services, including psychiatric treatment, housing, and community case management.

In general, treatment with antipsychotic medication requires awareness of HIV-infected patients' susceptibility to neuroleptic-induced EPS as a result of HIV-induced neuronal damage to the basal ganglia. Movement disorders (acute dystonia, parkinsonism, ataxia) can be seen in advanced HIV disease in the absence of antipsychotic exposure. General recommendations include avoidance of high-potency D2 blocking agents (eg, haloperidol),

avoidance of depot neuroleptics, and the consideration that maintenance antipsychotic medication may not be necessary for the complete remission of new-onset or transient psychotic symptoms. Most clinicians prefer the use of atypical antipsychotics in this population; however, they are associated with development of metabolic syndrome, cardiac problems, and obesity.[72]

A literature search on the use of antipsychotic medication in HIV-AIDS revealed 6 studies published since 1993; these studies described treatment of psychosis occurring in delirious, schizophrenic, and manic patients. Agents reported in the literature include haloperidol (mean dose, 3 mg),[73] clozapine (mean dose, 27 mg/d),[74] risperidone (mean dose, 3.3 mg/d),[75] and olanzapine (10–15 mg/d).[76] Haloperidol was reported to have a high incidence of EPS and caution is encouraged with clozapine because of the risk for agranulocytosis and interaction with ritonavir.

Anxiety

Anxiety is common in patients who are HIV-positive, estimated to occur in 22% to 47%. Generalized anxiety disorder has been found to range between 6.5% and 20.0% in HIV samples.[77, 78] Posttraumatic stress disorder is a common anxiety disorder in persons with HIV, estimated at 10% to 54% among populations such as men who have sex with men, minority women, and those with persistent pain.[79, 80] Patients who are HIV positive with subclinical or overt neurocognitive impairment are more sensitive to the side effects of anxiolytic medications and should start at low doses. Drug-drug interactions have been reported with anxiolytics and AIDS medications; for example, there are case reports of patients who are HIV-positive on protease inhibitors who experienced prolonged sedation when given midazolam.[81] Buspirone, a popular antianxiety agent and 5HT1A agonist, has been reported to cause extrapyramidal signs when given with protease inhibitors such as ritonavir.[82] Anxiety also interferes with ART adherence.[83]

Members of the Organization of AIDS Psychiatry participated in a Web-based survey. Consensus emerged regarding first-line treatment for depression (escitalopram/ citalopram), for psychosis and secondary mania (quetiapine), and for anxiety (clonazepam).[84]

Herpes Simplex Encephalitis

Several viruses can cause viral encephalitis including HSV.[85] HSV is the etiologic agent for herpes simplex encephalitis (HSE), the most common source of acute viral encephalitis in the United States, with an annual incidence of 2000 cases yearly.[85, 86] Two principal forms of HSV exist: HSV-1, which typically leads to orolabial lesions; and HSV-2, which is responsible for genital herpes lesions. HSV-2 infections more typically result in aseptic meningitis, whereas HSV-1 causes HSE. HSE is a potentially lethal infection with a mortality rate of up to 70% if left untreated and 14% to 20% with treatment. [85, 87] Half of HSE cases occur in people older than 50, whereas a third of cases are in people younger than 20.[88]

Clinically, HSE often presents with acute onset of symptoms, such as fever, altered mental status, seizures, and focal neurologic signs, such as aphasia and hemiparesis. Without treatment, patients may progress to coma.[86] Before the acute presentation, there may be a

prodrome characterized by headache, fatigue, mild fever, and irritability. It is hypothesized that HSV-1 enters the brain via the olfactory nerves and spreads into the limbic system, frontal, and temporal lobes. Infected neurons and other cells can undergo cytolysis, causing hemorrhagic destruction of brain tissue. Particularly vulnerable areas include the fronto-orbital region, temporal lobes, hippocampus, cingulate gyrus, and insular cortex.[89]

HSE leaves up to 80% of people who survive infection with a number of residual cognitive and neuropsychiatric sequelae.[85] Cognitively, patients may experience significant limitations in anterograde memory formation with additional impairment in retrograde memory. The cognitive effects of HSE are dependent on the sites of the brain involved. Although HSV-1 infection is often bilateral, impairments seen clinically may be dependent on lateralization of HSV-1–related brain injuries. In particular, right hemispheric involvement often leads to subtle deficits with less functional impairment. Left hemispheric neuronal damage, however, creates difficulties in language function and verbal memory.[85] Additional impairments, such as semantic aphasia or mutism, are found in up to 46% of patients with HSE and, more rarely, auditory agnosia also has been documented.[85, 86] Long-term consequences of HSE include memory impairment and behavioral and personality changes.[85] Neuropsychiatrically, patients may exhibit symptoms of aggression and disinhibition consistent with a Klüver-Bucy syndrome. Early treatment may ameliorate some of these symptoms; however, particularly in the young and old, cognitive impairments secondary to HSE may lead to postencephalitic dementia.[85, 90]

HSE is diagnosed by using a combination of clinical features and laboratory and imaging findings (Table 3). Noncontrast CT imaging demonstrates abnormalities in up to 50% of scans, including a midline shift. MRI, however, remains the most sensitive imaging tool in diagnosing HSE and is recommended as the first diagnostic step after the clinical examination.[86] MRI findings include focal hyperintensities on T2-weighted imaging. Electroencephalography (EEG) also may be used and initially may show some generalized or focal slowing over the temporal lobes (sites that are commonly a focus for HSV-1 infection), but may change to lateralized, epileptiform activity.[85] Lumbar puncture may demonstrate an elevated opening pressure, CSF leukocytosis, and xanthochromia in addition to a normal CSF glucose level. Polymerase chain reaction demonstrates the presence of HSV-1 infection in the CSF.

HSE is treated with intravenous acyclovir (60 mg/kg per day, given in 3 divided doses) for 21 days.[91] A repeat CSF examination should be performed at the end of therapy to ensure that the virus has cleared. The use of continued outpatient treatment with oral valacyclovir is common but has not been shown to improve outcomes.[92] Recovery is determined in part by how quickly treatment is begun, with increased morbidity and mortality associated with delays in treatment.[88] Although acyclovir treatment of HSV infection in HSE is widely accepted, there is no well-defined treatment specific for the cognitive and neuropsychiatric symptoms associated with HSE. It has been proposed that using dopamine antagonists in a carefully monitored manner may be useful in treating the behavioral disturbances associated with HSE in the acute period. This is based on evidence from an animal study suggesting activation of the mesostriatal dopamine system in HSE. Other treatments used in clinical

practice for the neurobehavioral sequelae of HSE include anticonvulsants, benzodiazepines, antipsychotics, stimulants, mood stabilizers, and cholinesterase inhibitors.[85, 93]

PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDERS ASSOCIATED WITH STREPTOCOCCAL INFECTIONS

Over the past 25 years, there has been mounting evidence for connections between group A b-hemolytic streptococcal (GAS) infections and the development of neuropsychiatric symptoms. Sir William Osler made the original observation that patients with Sydenham chorea, a complication of GAS infection, also exhibited behaviors consistent with tics and obsessive-compulsive disorder (OCD). Later work demonstrated that as many as 70% to 80% of patients with Sydenham chorea also have clinical features meeting diagnostic criteria for OCD, particularly in children.[94, 95] Based on work with children who exhibited abrupt onset of OCD symptoms or tics following GAS infection, the development of these symptoms was linked to an immune system–mediated response to the original infection, termed “pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections” (PANDAS).[94, 96] Age of symptom onset is approximately 3 years younger in PANDAS than childhood-onset OCD. Additionally, the abrupt onset and relapsing-remitting pattern of symptoms in PANDAS differs from the more gradual onset and chronic pattern in childhood OCD.[95, 97] There may be a heritable component to PANDAS, because children with PANDAS have parents and grandparents with significantly higher rates of streptococcal infection complications, such as rheumatic fever, compared with controls.[96]

Diagnostic criteria for PANDAS include (1) age of onset between the ages of 3 and 11 years; (2) meeting criteria for OCD or a tic disorder; (3) episodic severity of symptoms; (4) association with GAS infection; and (5) association with neurologic abnormalities, including hyperactivity, tic, or choreoform movements.[94, 95] Although resembling childhood-onset OCD, PANDAS is distinguished clinically by a distinct temporal relationship between a GAS infection and onset of OCD or tics.

Experts convened at the National Institutes of Health in July 2010, given the agreement that a subgroup of children with OCD have an abrupt onset of symptoms accompanied by a variety of severe and acute neuropsychiatric symptoms. Given the ongoing controversy about the etiology of the symptoms, experts proposed an expanded clinical syndrome, pediatric acute-onset neuropsychiatric syndrome (PANS) or childhood acute neuropsychiatric symptoms (CANS), which may be caused by noninfectious (eg, drugs, metabolic abnormalities) or infectious (eg, group A streptococci) triggers. Proposed diagnostic criteria for PANS/CANS include the following:

- Abrupt, dramatic onset of OCD or severely restricted food intake
- At least 2 concurrent severe neuropsychiatric symptoms (eg, anxiety, depression, emotional lability), also with acute onset
- Symptoms not better explained by a known neurologic or medical disorder (for example, Sydenham chorea, systemic lupus erythematosus, Tourette disorder)[98, 99]

To make a more definitive diagnosis (see Table 3), obtaining antistreptococcal antibody titers (including antistreptolysin O [ASO] and antideoxyribonuclease B [ADB] antibodies) that rise during a symptomatic exacerbation and fall with symptomatic improvement is often needed. Serologic diagnosis of recent GAS infection can be made by demonstrating a 0.2 log10 rise (a 58% increase) in either ASO or ADB, ordinarily obtained 4 to 8 weeks apart, although only 62% of new GAS acquisitions were followed by such a rise. A single high titer, rather than serial acute and convalescent titers, is not diagnostically reliable, but may be considered contributory if levels exceed twofold (0.3 log10) above the laboratory's stated upper limit of normal, because these higher levels are uncommon in children without recent streptococcal infection.[100] Use of these antistreptococcal antibody titers, however, is complicated because titers may remain high for months after infection.[95] There is also evidence that antibodies directed against the basal ganglia are found more commonly in patients with PANDAS relative to people with uncomplicated streptococcal infections.[101] This finding may shed further light on the pathophysiology of PANDAS, given that preliminary MRI suggests basal ganglia enlargement in patients with PANDAS.[102] In determining susceptibility to PANDAS, studies have indicated that patients with PANDAS are more likely to also have lymphocytes that are positive for the D8/17 marker. This B-lymphocyte alloantigen marker is also associated with other streptococcal-related conditions, such as rheumatic fever and Sydenham chorea, further suggesting an immune basis.[94, 95]

Ultimately, based on the clinical and diagnostic features of PANDAS, it has been suggested that the pathophysiology of PANDAS is based on the development of an autoimmune reaction in patients who are susceptible (ie, based on family history, immunologic markers). This reaction occurs in response to infection with GAS in which the immune system inappropriately generates antibodies against epitopes on the basal ganglia that resemble streptococcal antigens through the process of molecular mimicry.[95] The resulting immune-mediated inflammatory process in the basal ganglia then may lead to the clinical features of PANDAS.[96]

Most instances of PANS are suspected to be postinfectious in origin, although no single microbe other than GAS has yet been consistently associated with the onset of PANS. Therefore, a detailed review and documentation of associated febrile and nonfebrile infectious illnesses, including signs and symptoms and diagnostic testing, is advised. The most commonly observed antecedent infection seems to be upper respiratory infection, including rhinosinusitis, pharyngitis, or bronchitis. It is not yet clear if any 1 of those 3 presentations is more likely than the others to be associated with the initiation of PANS. *Mycoplasma pneumoniae*, influenza, Epstein-Barr virus, and Lyme disease have been implicated to PANS onset or flares.[103]

Treatment of PANDAS has been largely based on immunomodulatory therapies. Notably, significant symptomatic improvements have been demonstrated in patients following use of plasma exchange and intravenous immunoglobulin (IVIG). In one study, severity of OCD symptoms diminished by 45% to 58% following treatment with either plasma exchange or IVIG.[96, 104] Despite this, immunomodulatory therapies have not been recommended as the routine treatment of PANDAS.[95] IVIG and plasma exchange both carry a substantial risk of adverse effects, and use of these modalities should be reserved for children with particularly

severe symptoms and a clear-cut PANDAS presentation.[105] The US National Institutes of Health and American Academy of Neurology 2011 guidelines state there are inadequate data to determine the efficacy of plasmapheresis in the treatment of acute OCD and tic symptoms in the setting of PANDAS and insufficient evidence to support or refute the use of plasmapheresis in the treatment of acute OCD and tic symptoms in the setting of PANDAS.[106] Use of antibiotic prophylaxis to prevent neuropsychiatric exacerbations following recurrent streptococcal infections has yielded mixed results. Although one double-blind, placebo- controlled trial found no benefit over placebo in preventing PANDAS exacerbations, another trial found that either penicillin or azithromycin were able not only to lower rates of streptococcal infections but also to decrease symptom exacerbations in patients with PANDAS.[107, 108] Evidence is insufficient to determine if tonsillectomy is effective.[109]

Children with OCD and/or tic disorders should receive standard neuropsychiatric treatment for these disorders (whether or not the children have evidence of recent GAS infection).[110, 111] Treatment of neuropsychiatric symptoms should not be delayed pending confirmation of PANDAS (eg, documenting rise in antistreptococcal antibodies or while monitoring for a second episode).

The neuropsychiatric manifestations of children in the PANDAS subgroup respond to treatment with standard pharmacologic and behavior therapies.[110] OCD symptoms generally respond to a combination of pharmacotherapy (typically a selective serotonin reuptake inhibitor) and cognitive behavior therapy. Motor and vocal tics can be treated with a variety of medications.

NEUROCYSTICERCOSIS

Neurocysticercosis (NCC) is the most common parasitic disease of the nervous system, particularly in developing countries in Asia, Latin America, and Africa. Because of rising rates of immigration from areas in which it is more prevalent, however, NCC is appearing more frequently in North America and Europe. Annually, more than 50,000 deaths worldwide are attributable to NCC. Even more patients are left alive with chronic, irreversible brain damage. Moreover, NCC is the major etiology for acquired epilepsy in endemic areas.[112] NCC is caused by infection with the tapeworm *Taenia solium*. Humans are the definitive host for *T solium*, whereas pigs serve as the intermediate host. NCC results generally from fecal-oral transmission in which people ingest the eggs of the tapeworm from contaminated food or water. Commonly, this route of transmission occurs through handling of food by others already infected or from improperly cleaned food. Autoinfection also occurs, albeit less frequently.[95] Once in the intestine, the eggs hatch and migrate throughout the body by way of the bloodstream, ultimately depositing into various tissues where they develop into the larval cysticercus form. When the site of larval deposition is in the CNS, NCC develops. Symptoms of NCC are dependent on the area and extent of nervous system involvement. The 4 main types of NCC are (1) parenchymal, (2) subarachnoid, (3) ventricular, and (4) spinal.[95]

Neurologically, seizures are the most common manifestation of NCC, occurring in 80% of infected patients, especially in the parenchymal form of the disease.[113] The seizures are typically simple partial or generalized tonic-clonic, although patients also may present with focal neurologic deficits based on the sites of infection. Stroke, intracranial hypertension, hydrocephalus, meningeal inflammation, fibrosis, or cyst formation also may occur.[112] As a result, NCC is on the differential diagnosis of most neurologic disorders in endemic regions.[114]

Given the varied neurologic presentations of NCC, it is not surprising that NCC also has many different psychiatric manifestations. Up to 15% of people infected with NCC exhibit only psychiatric sequelae.[115] In a study examining rates of *T solium* infection among chronic psychiatric inpatients in a community in Venezuela, 18.5% of the inpatients were infected versus 1.6% of controls.[116] Commonly, patients present with acute psychiatric decompensation,[95] mimicking psychotic states, such as schizophrenia. In one case report, NCC was marked by acute psychosis characterized by agitation, thought disorganization, paranoia, and auditory-visual hallucinations.[112, 117] Other psychiatric manifestations of NCC include depression or dementia; suspicion for NCC-related dementia ought to be high if it occurs in patients who are younger, also have a history of seizures, have acute onset of symptoms, and are from an area in which NCC is endemic.[95] In a recent study from Brazil, more than 80% of the patients with NCC reported depressive symptoms.[118]

The diagnosis of NCC is often difficult because the symptoms often resemble those from a broad differential of other disorders (see Table 3). NCC most commonly is diagnosed, however, from clinical history, imaging, and laboratory techniques. Besides biopsies that often prove difficult to do, brain imaging using CT and MRI scans allows for visualization of lesions from *Taenia* infection. In active disease, ring-enhancing lesions are most typically seen; visualization of the parasite's scolex within a cystic structure is pathognomonic for NCC.[112] Infection outside the brain parenchyma makes visualization more difficult.[95] Laboratory studies are often used to confirm the diagnosis by investigating patient serology for antibodies related to *Taenia* infection. Enzyme-linked immunosorbent assay and enzyme-linked immunoelectrotransfer are often used for antibody detection.[95] However, a weakness of the test is that it may be false negative in approximately 50% of patients with a single cerebral cyst or in those with calcifications alone. Another weakness is that it may be false positive in persons who had been exposed to the adult parasite without developing the disease.[119]

NCC treatment has been controversial, with few rigorous, large-scale studies conducted examining the various treatment options. The location of cysts; degree, size, and severity of local inflammation around lesions; and symptom severity all affect the treatment choice. This is complicated by findings that the treatments themselves may exacerbate the already present inflammatory response leading to symptomatic worsening.[120] Nevertheless, NCC has been treated for more than 20 years using anti-helminthic agents, such as praziquantel and albendazole.[95, 112, 120] Other agents may be given in concert with these drugs, including steroids (to treat pericystic inflammation and NCC-related encephalitis) and anticonvulsants (because of NCC-related seizures). The American Academy of Neurology issued a guideline document and concluded that albendazole plus corticosteroids should be considered for

patients with neurocysticercosis, as the use of these drugs reduces the number of viable cysts on control neuroimaging studies (level B of evidence) and the long-term risk of seizure recurrence (level B evidence).[121] In some instances, surgery also may be needed for placement of ventricular shunts to treat hydrocephalus secondary to arachnoiditis.[112, 120]

NEUROSYPHILIS

Cases of syphilis have been documented since the late 1400s and, with the HIV epidemic in recent years, have had global resurgence. By the 1920s, more than 20% of patients in American mental hospitals had tertiary neurosyphilis (NS).[122] With the advent of antibiotics, such as penicillin, the incidence and prevalence of syphilis and resultant NS dropped significantly; however, in parallel with the HIV epidemic, rates of infection (largely by sexual intercourse) began to rise again. There has been an 81% increase in cases of syphilis infection among men since 2000, with an annual incidence of 0.2 to 2.1 cases per 100,000 immunocompetent individuals. [122–124] This has been an important health problem because syphilis facilitates coinfection with HIV.[124] HIV causes impaired cell-mediated immunity, which accelerates the progression of syphilis, so that patients with HIV have a greater frequency of neurosyphilis.[125]

Known as the original “great imitator,” syphilis has a number of presentations in virtually all organ systems, including the CNS. Consequently, NS has been linked with a diverse array of cognitive and psychiatric syndromes. Untreated, symptomatic NS develops in 4% to 9% of patients infected with syphilis.[126]

NS is caused by *Treponema pallidum*, the spirochete responsible for syphilis. Infection may be either symptomatic or asymptomatic. Although NS classically presented with tabes dorsalis or general paresis, these are less common today. Instead, patients with NS are asymptomatic or may present with seizures, ocular symptoms, or with psychiatric and behavioral changes.[122] Early NS may occur within 5 years of infection, whereas late NS (involving the brain parenchyma) typically occurs within 5 to 25 years of infection. HIV infection, however, may accelerate the clinical progression to symptomatic NS.[126] The general paresis form of NS is the type most commonly associated with psychiatric symptoms.[122] The psychiatric presentation of NS typically begins insidiously, with mood changes including symptoms of mania or depression. Up to 27% of patients with the general paresis form of NS develop depression characterized by melancholia, suicidal ideation, and psychomotor retardation. Patients also may present with psychosis of acute or insidious onset that may mimic schizophrenia.[127] Personality changes in patients with NS can include emotional lability, antisocial behaviors, anhedonia, social withdrawal, explosive temper, giddiness, hypersexuality, or less attention to personal details. As NS progresses, however, intellectual functioning worsens. Ultimately, symptoms of dementia predominate, leading to disability and, finally, death.[122, 127] NS often leads to cortical atrophy and brain lesions. Lesions imaged by MRI in the temporoparietal region have been associated with cognitive impairments as measured by the Mini Mental-State Examination, whereas lesions in the frontal lobes are associated with overall psychiatric morbidity.[128] Importantly, although prompt treatment of NS is necessary to halt the progression of the illness, it is not expected that patients’ mental status will improve completely, because of neuronal loss.[122]

Diagnosis of NS is difficult, because unlike other infectious organisms, *T pallidum* cannot be grown in culture (see Table 3). Because so many cases of NS are asymptomatic, many infected patients are missed. If the index of suspicion is sufficiently high, however, NS is diagnosed serologically by the rapid plasma regain and Venereal Disease Research Laboratory tests; CSF may be used in the Venereal Disease Research Laboratory assay. If positive, results are confirmed with a microhemagglutination assay for *T pallidum* or with the fluorescent treponemal antibody-absorption assay.[122]

NS is treated with a 10-day to 14-day course of aqueous penicillin G (18–24 million units per day with 3–4 million units given intravenously every 4 hours). An alternative is to treat the patient with procaine penicillin (2.4 million units daily intramuscularly) combined with probenecid, 500 mg orally, 4 times daily, particularly if compliant with treatment; ceftriaxone may be used if the patient is allergic to penicillin.[122, 124] Sexual partners of the patient also may need evaluation and treatment.[112] There has been little documentation specifically addressing treatment of psychiatric symptoms associated with NS. There is no consensus that antibiotic treatment of neurosyphilis produces a persistent improvement in cognition in persons with general paresis.[129] A recent study by Sanchez and Zisselman[124] recommended use of a typical antipsychotic, haloperidol, or the atypical agents, quetiapine or risperidone, to treat psychosis in patients with NS. An anticonvulsant, such as divalproex sodium, also was recommended to address agitation and for mood stabilization.[124] Smaller case reports supported atypical antipsychotics, such as olanzapine and quetiapine, in treatment of NS-associated psychosis.[130, 131]

CREUTZFELDT-JAKOB DISEASE

Prion disorders have received much attention in the media given recent epidemics of bovine spongiform encephalopathy (also known as “mad cow disease”) and the resulting health risks associated with possible transmission to humans. There are several diseases caused by the prion protein, a novel infectious agent composed of a protein ordinarily found in all humans. These diseases are known as “transmissible spongiform encephalopathies” and are found in many mammals, including cattle, in the form of bovine spongiform encephalopathy, in sheep (known as “scrapie”), and in humans. Prion diseases are believed to occur when the naturally occurring form of the prion protein acquires an abnormal conformational state that facilitates conversion of surrounding prion protein into the pathogenic form, ultimately leading to cell death.[132] In the CNS, this process leads to marked neurodegeneration causing spongiform changes, and, consequently, a reactive astrocytosis.[133]

Prion disease in humans was first noted in 1920 and 1921 by H G. Creutzfeldt and A.M. Jacob, respectively.[134] Human prion diseases occur in most of the developed world at a rate of 1.0 to 1.5 cases per million per year. In the United States, with a population of approximately 330 million, approximately 400 cases of prion disease are diagnosed per year, an incidence of 1.2 in 1.0 million. Of human prion diseases, 80% to 95% are sporadic Creutzfeldt-Jakob disease (CJD), 10% to 15% are genetic (often familial), and fewer than 1% are acquired.[135] Four forms of CJD exist: (1) sporadic CJD, (2) familial CJD, (3) variant CJD, and (4) iatrogenic CJD. Most CJD cases are sporadic in nature, constituting up to 80%

to 95% of all reported CJD.[135] Sporadic CJD reportedly has a mean survival of approximately 6 months (median approximately 5 months), with 85% to 90% of patients dying within 1 year. The peak age of onset is 55 to 75 years of age, with median age of onset of approximately 67 years and mean of 64 years.[136, 137] In sporadic CJD, the misfolding of the prion protein occurs likely because of a spontaneous mutation in the gene encoding the prion protein. Although the precise significance relating to pathogenesis is unknown, up to 85% of patients with sporadic CJD are homozygote for 2 copies of the methionine amino acid at codon 129 of the prion protein (Met/Met).[134]

Up to 10% to 15% of CJD cases are familial in origin. Genetic prion diseases historically have been divided into 3 forms based on clinicopathologic features: familial CJD, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia. Familial CJD is inherited in an autosomal-dominant fashion. Most mutations causing genetic prion disease are caused by missense mutations, but several octapeptide repeat insertion mutations and at least 5 stop codon mutations exist.[138] Among the groups with the highest prevalence of familial CJD are Libyan Jews and clusters of families in Chile, Slovakia, Japan, and the United States.

Variant CJD (also known as “new-variant CJD”) was first described in 1996 after several CJD cases in the United Kingdom were identified as having features that varied from the classic presentation of sporadic CJD. It is the only form of human prion disease known to be transmitted directly from animals to humans, in most cases through exposure to bovine spongiform encephalopathy.[139] It occurred because of the practice of feeding sheep products, some of which were unfortunately contaminated with the prion disease scrapie, to cattle, mostly in the United Kingdom but in other countries as well.[139, 140] Food products derived from these infected cattle were consumed by humans, a portion of whom developed variant CJD. The clinical presentation of variant CJD usually begins with a psychiatric prodrome, often at least 6 months before the onset of traditional neurologic symptoms; cognitive dysfunction, dysesthesia, cerebellar dysfunction, and involuntary movements (eg, dystonia, myoclonus, or chorea) usually appear several months after psychiatric onset. Compared with sporadic CJD, the median age of onset of patients with variant CJD is much younger than most sporadic cases, approximately 27 years (range 12–74 years), with a longer median disease duration of 14.5 months.[140] Variant CJD also may be transmissible by blood, including transfusions.[133, 134]

Last, iatrogenic CJD has been documented after exposure to tissues from patients infected with CJD or from surgical instruments that have come into contact with those infected. Cases have been reported of patients developing CJD after corneal transplantation or dura mater grafts from infected donors and by cadaveric pituitary growth hormone.[134] Clinically, sporadic CJD presents as a rapidly progressive dementia with average disease duration of only 1 year until death. Moreover, the neurologic and neuropsychiatric symptoms associated with CJD often mimic those found in other dementias, such as Alzheimer disease or Lewy body dementia. Common neurologic symptoms may include extrapyramidal signs, cerebellar ataxia, sensory complaints, myoclonus, and dysphagia. In advanced stages of illness, patients can exhibit akinetic mutism and may ultimately die from aspiration pneumonia.[132] Although sporadic CJD was classically believed to present with primarily

neurologic manifestations with some psychiatric symptoms appearing late in the course of illness, more recently it has been demonstrated that psychiatric symptoms commonly occur at diagnosis and throughout progression of the disease. A retrospective review of 126 patients with sporadic CJD at the Mayo Clinic revealed that 80% of the cases demonstrated psychiatric symptoms within the first 100 days of illness, with 26% occurring at presentation.[141] In contrast to sporadic CJD, psychiatric and neuropsychiatric symptoms are often the most prominent aspects in the clinical presentation of variant CJD.[141]

Psychiatric sequelae of CJD include depressed mood and apathy.[142] A prodromal phase has been described characterized by fatigue, weight loss, impaired sleep, poor judgment, and unusual behavior. Patients also may display unusually intense emotional responses; anxiety; agitation; and psychotic symptoms, such as delusions and hallucinations.[141, 143] At times, presentations of primarily depression or psychosis in CJD have made it difficult to distinguish from primary psychiatric disorders and led to misdiagnosis or delays in diagnosis of CJD.[144] Neuropsychologic testing revealed focal cortical deficits in sporadic CJD in contrast to more generalized deficits in variant CJD.[145]

Based on criteria suggested by the World Health Organization, definite diagnosis of sporadic CJD involves either neuropathologic examination or detection of the pathogenic scrapie form of the prion protein in brain samples by Western blot (see Table 3).[146] To receive a probable diagnosis of sporadic CJD, patients must have 2 of the following clinical signs: (1) cerebellar or visual signs; (2) myoclonus, pyramidal, or extrapyramidal signs; or (3) akinetic mutism. Additionally, patients must have detection of the 14-3-3 protein in the CSF or an EEG consistent with CJD coupled with disease duration leading to death in less than 2 years, or investigation not suggestive of an alternative diagnosis.[132]

Besides use of clinical symptoms, diagnosis is also based on EEG, imaging, and laboratory findings. Typical EEG findings in sporadic CJD include periodic sharp wave complexes that have either biphasic or triphasic waves or complexes with mixed spikes. In contrast, EEGs of patients with variant CJD do not show periodic sharp wave complexes, but rather have nonspecific slow-wave activity.[146] MRI has been used extensively in diagnosis of CJD. There are abnormalities in the basal ganglia and cortex and a unique pattern of “cortical ribboning.” Patients with variant CJD prominently display a pattern of hyperintensity in the pulvinar thalami.[132] In applying laboratory testing for diagnosis, the detection of the 14-3-3 protein in the CSF of patients with CJD is both quite sensitive and specific for the sporadic form of the disease, although less so in the variant form.[147] A clear diagnosis of variant CJD also may be made by tonsil biopsy through detection of the scrapie form of the prion protein.[148]

Presently, there is no effective treatment for CJD. A focus of potential treatment strategies has been to block accumulation of the pathogenic scrapie form of the prion protein. The antimalarial agent quinacrine and the phenothiazines have been tried with little success in animal and human trials. Another recent approach has been development of vaccines to develop antibodies against the prion protein, although the results of these efforts have been unclear thus far.[133]

Lyme disease, caused by infection with the tic-borne spirochete *Borrelia burgdorferi*, has been associated with a variety of manifestations, including neuropsychiatric symptoms, or neuroborreliosis. Over the past 20 years, there has been significant controversy regarding the neuropsychiatric manifestations of neuroborreliosis, which is related to the fact that symptoms are often nonspecific (fatigue, sleep disturbance, generalized cognitive complaints, low mood, all symptoms of depression); serologic testing may show evidence of prior systemic exposure but cannot determine whether or not there is acute disease; and symptoms may persist after acute antibiotic treatment. [149, 150] Further, the mechanisms of the neuropsychiatric manifestations are not precisely known, being possibly related to direct CNS infection with the organism, to acute or long-term inflammatory processes associated with systemic or CNS infection, or some combination of these. Over the past 10 years, there is accumulating evidence that *B burgdorferi* may adhere to endothelial cells at the blood-brain barrier, causing vasculitis and increased blood-brain barrier permeability, leading to CNS invasion and adherence to astrocytes, resulting in a deleterious inflammatory cascade.[151] The resulting changes in the CNS, including abnormalities in subcortical frontotemporal white matter and basal ganglia functioning,[152] may explain the more chronic neuropsychiatric symptoms and why antibiotic treatment of these chronic symptoms is generally not associated with improvement in symptoms or CNS pathology.[149–151]

In the early stages of acute Lyme disease, patients may present with meningitis, cranial neuritis, and radiculoneuritis.[150] In many such cases, there are positive CSF findings for *B burgdorferi* antibody (immunoglobulin G) and elevated protein. Cognitive deficits associated with acute and chronic Lyme disease include poor attention and concentration, impaired verbal memory, word-finding difficulties, psychomotor slowing, and executive dysfunction, all consistent with subcortical-frontal pathology. Interestingly, study of patients with Lyme disease with chronic cognitive complaints indicates that those with abnormal CSF are more likely than those with normal CSF to have actual neuropsychologic deficits. In those with normal CSF, cognitive complaints are more likely to be associated with concurrent depression.[150] Psychiatrically, patients with both acute and chronic symptoms of neuroborreliosis may present with depression, mood lability, irritability, anxiety, panic attacks, and more rarely, mania, psychosis, and obsessive-compulsive symptoms.[152] There are no large-scale well-controlled studies, however, to suggest that patients with Lyme disease have a greater burden of such symptoms than the general population.

In terms of diagnosis, neurologic examination is usually nonfocal. Bedside cognitive evaluation may be normal to mildly abnormal and more extensive neuropsychologic testing may be necessary to detect the characteristic deficits mentioned previously. Lumbar puncture and CSF evaluation may reveal *B burgdorferi* DNA detected by polymerase chain reaction and antibody to *B burgdorferi*, nonspecific protein elevation, and CSF pleocytosis. The CSF may be normal, however, in a substantial number of cases. Standard structural neuroimaging, including brain CT or MRI with contrast, is often normal in both the acute and chronic stages of the disease. Quantitative single-photon emission CT of the brain has proved more useful in detecting abnormality, including hypoperfusion in frontal subcortical and cortical regions.[153] This method has been used to follow response to antibiotic treatment.

In terms of treatment, intravenous infusion of ceftriaxone, 2 g daily for 30 days, followed by oral doxycycline, 200 mg daily for 60 days, has been tested.[149] Other regimens in the literature include intravenous penicillin or a derivative, amoxicillin. Although such regimens have been helpful for neuroborreliosis with clear evidence of abnormal CSF in acute and chronic disease, results have been less favorable in patients with chronic symptoms and minimal objective evidence of CNS infection.

In terms of psychotropic medication treatment for psychiatric comorbidities, the literature is quite sparse. Treatment is generally symptomatic, addressing symptoms of depression (ie, with selective serotonin reuptake inhibitors), fatigue and cognitive complaints (ie, with psychostimulants or modafinil), and mood lability and psychosis (ie, with atypical neuroleptics). Given the subcortical involvement of the spirochete, however, it is important to assess for extrapyramidal side effects with the use of atypical neuroleptic medications.

SUMMARY

This article reviews the clinical characteristics and treatment of a number of infectious diseases that have prominent neuropsychiatric manifestations. Although each entity has unique characteristics, there are several common themes that are important for clinicians to remember. First, maintain an index of suspicion, especially when patients present with new-onset psychiatric symptoms without a history of prior psychiatric illness. It is commonplace to overlook medical or neurologic illness in assuming a primary psychiatric diagnosis, including sexual risk behavior, blood-borne exposures, and travel history. Third, although a thorough diagnostic workup is necessary to identify and treat the infection, equally important is a full characterization of the psychiatric and cognitive symptoms associated with the infection so as to track the effects of treatment. This becomes particularly important when patients have residual deficits that affect everyday function and ability to work. Finally, it is important to remember that concurrent treatment with antibiotics and psychotropic medications is often necessary. For most of these infectious diseases, formal study of psychotropic medications is relatively infrequent, so clinicians should be vigilant regarding potential drug-drug and drug-disease interactions. Fortunately, when these principles are followed, neuropsychiatric manifestations of infectious diseases can be successfully identified and treated.

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Box 1 Differential diagnosis of psychiatric disorders and symptoms in medical inpatients with HIVAIDS

- Primary psychiatric disorder
- CNS HIV infection (minor neurocognitive disorder and HIV-associated dementia)
- CNS opportunistic illnesses and cancers (see Table 2)
- Substance intoxication and withdrawal
- Neuropsychiatric complications of hepatitis C and its treatments
- Neuropsychiatric side effects of HIV medications
- Drug-drug interactions
- Endocrine abnormalities (eg, hypogonadism, adrenal insufficiency, thyroid disease)

Abbreviations: CNS, central nervous system; HIV, human immunodeficiency virus.

Box 2 Diagnostic evaluation of the medical inpatient with HIV-AIDS and neuropsychiatric disturbances

- Medical evaluation with screening laboratories: complete blood count, chemistry screen (including liver and renal function tests), urinalysis, chest radiograph, electrocardiogram, blood and urine cultures (when applicable)
- Psychiatric diagnostic interview including personal and family history
- Cognitive screen (HIV Dementia Scale)
- Additional laboratories when applicable: illicit drug toxicology screen, serum psychotropic drug levels, thyroid function tests, antithyroid antibodies, vitamin B12 and B6 levels, total or bioavailable testosterone, dehydroepiandrosterone sulfate, adrenocorticotropic stimulation test, 24-hour urine cortisol
- Evaluation for hepatitis C (including viral load)
- Review of antiretroviral regimen for neuropsychiatric side effects
- Review of psychotropic mediations for efficacy, neuropsychiatric side effects, drug interactions
- Neuroimaging (MRI, magnetic resonance spectroscopy)
- Lumbar puncture

KEY POINTS

- Among the critically ill, infectious diseases can play a significant role in the etiology of neuropsychiatric disturbances.
- All critical care physicians are familiar with delirium as a secondary complication of systemic infection.
- This article focuses on key infectious diseases that commonly and directly produce neuropsychiatric symptoms, including direct infection of the central nervous system, human immunodeficiency virus infection, and AIDS.

Table 1

Frequency of psychiatric disorders reported in the inpatient medical setting

Authors	n	% Male	HIV Risk	Medical Illnesses	Depressive Disorders	% Dementia	% Delirium	% Substance Use Disorder	% Other Psychiatric Disorders
Perry & Tross,[7] 1984	52 AIDS	98	Homosexual 79% Homosexual + IVDU 12% Other 9%	OI 71% KS 17% OI + KS 12%	Any 83%	11	29	11	Schizophrenia 2
Dilley et al,[8] 1985	13 AIDS	100	Homosexual 100%	OI 70% OI + KS 15% Other 15%	Adjustment disorder 54% MDD 15%	8	8	31	Panic 8
O'Dowd & Mc Kegney,[9] 1990	67 AIDS	69	Not reported	Not reported	Adjustment disorder 42% MDD 3%	22	27	20	Axis II 6
Bialer et al,[10] 1996	433 AIDS 116 HIV+	79	Not reported	Not reported	Organic mood 13%	22	29	36	Axis II 9
Ferrando et al,[48] 1997	36 AIDS 4 HIV+	60	Homosexual 34% IVDU 31% Heterosexual 31%	OI 89%	Adjustment disorder 13% MDD 1% MDD or 31% dysthymic disorder	19	19	19	Mania/hypomania 11 Anxiety 8

Abbreviations: HIV, human immunodeficiency virus; IVDU, intravenous drug user; KS, Kaposi sarcoma; MDD, major depressive disorder; OI, opportunistic illnesses.

Table 2

Opportunistic illnesses of the central nervous system in AIDS

OI	CD4	Signs	Focal	CT/MRI	Lumbar Puncture
Toxoplasmosis	<100	Fever	Y	Ring-enhancing lesions	*Toxoplasma gondii* antibody or PCR High specificity/low sensitivity
		Delirium		Basal ganglia	Other routine CSF studies not generally diagnostic
		Headache		Gray-white junction	
		Seizures			
Cytomegalovirus	<50	Delirium	Y/N	Ventricular enlargement	CMV PCR
		Infections found at diagnosis		Increased periventricular signal (T2 image)	Variable specificity/variable sensitivity
		Retina			Elevated protein level, pleocytosis, hypoglycorrhachia
		Blood			
		Adrenal gland			
		Gastrointestinal tract			
Cryptococcal meningitis	<100	Fever	N	Nonspecific	*Cryptococcus neoformans*, India ink, latex agglutination or PCR
		Delirium			High specificity/high sensitivity
		Not universally seen			Other routine CSF studies not generally diagnostic
		Increased intracranial pressure (50%)			
		Seizures			
Progressive multifocal leukoencephalopathy (JCV)	<100	Mono/hemiparesis Dysarthria	Y	Attenuated signal/(T2 images)	JCV PCR
		Gait disturbance Sensory deficit Progressive dementia Occasional		Periventricular White matter	High specificity/high sensitivity
		Visual loss Seizures		Other areas: Gray matter	Other routine CSF studies not generally diagnostic
				Brainstem Cerebellum Spinal cord	
Central nervous system neoplasm/lymphoma	<100	Afebrile delirium Seizures (10%) Increased intracranial pressure	Y	Lesions Hypodense/patchy Nodular Enhancing SPECT thallium	EBV PCR
				differentiates from toxoplasmosis	High specificity/high sensitivity
					Other routine CSF studies not generally diagnostic

Abbreviations: CMV, cytomegalovirus; CSF, cerebrospinal fluid; CT, computed tomography; EBV, Epstein-Barr virus; JCV, JC virus; N, no; OI, opportunistic illnesses; PCR, polymerase chain reaction; SPECT, single-photon emission computed tomography; Y, yes.

Crit Care Clin. Author manuscript; available in PMC 2018 January 17.

Table 3

Clinical features and diagnosis of non-HIV infectious diseases with neuropsychiatric manifestations

Disease	Signs	Focal	CT/MRI	Laboratory Tests	Neuropsychiatric Sequelae	Treatment
Herpes encephalitis	Fever	Yes	Midline shift	EEG	Difficulties in language function and verbal memory	Intravenous acyclovir
	Altered mental Status		T2 focal hyperintensities	Lumbar puncture	Semantic aphasia or autism	
	Focal neurologic Signs			PCR	Behavioral and personality changes	
	Seizures				Klüver-Bucy syndrome	
	Aggression/ disinhibition					
	Language impairments					
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections	Age of onset between ages 3 and 11 y	No	Basal ganglia enlargement	Antistreptococcal antibody titers	OCD or tic disorder symptoms	Plasma exchange intravenous immunoglobulin
	OCD or tic disorder symptoms			ESR, CRP	Other movement disorders	±PCN or azithromycin
	Temporal association between symptoms and group A-hemolytic streptococcal infection			D8/17 B-lymphocyte marker		
				↑antibasal ganglia Ab's		
Neurocysticercosis	Seizures	Yes	Ring-enhancing lesions	ELISA EITB	Seizures	Antihelminthic agents: praziquantel, albendazole
	Agitation		Visualization of scolex in cystic structure		Psychosislike states	Steroids Anticonvulsants
	Psychosis				Dementia	
	Focal neurologic signs					
	Depression					
	Dementia					
Neurosyphilis	General paresis	No	Lesions correlate to specific deficits	VDRL	Mood disorders	PCN
	Psychosis			Rapid plasma regain	Psychosislike states	Ceftriaxone
	Emotional lability			Fluorescent treponemal antibody-absorption assay	Behavioral changes: disinhibition	
	Anhedonia			Lumbar puncture	Dementia	
	Social withdrawal					
	Dementia					

Disease	Signs	Focal	CT/MRI	Laboratory Tests	Neuropsychiatric Sequelae	Treatment
Creutzfeldt-Jakob disease	Rapidly progressive cognitive decline	No	Cortical ribboning	EEG: periodic sharp wave complexes	Rapidly progressive dementia	No effective treatment has been identified
	Extrapyramidal signs, ataxia, myoclonus, dysphagia		Basal ganglia and cortical abnormalities	Tonsil biopsy for variant	Cerebellar signs	
	Akinetic mutism		Variant Creutzfeldt-Jakob disease: hyperintensity in pulvinar thalami	Creutzfeldt-Jakob disease	Visual signs	
	Agitation			14-3-3 assay	Myoclonus	
	Psychosis				Pyramidal symptoms	
	Depression				Extrapyramidal symptoms	
					Akinetic mutism	
					Mood disorders	
					Psychosislike states	

Abbreviations: ↑, increasing; Ab, antibody; CRP, C-reactive protein; CT, computed tomography; EEG, electroencephalogram; EITB, enzyme-linked immunoelectron-transfer; ELISA, enzyme-linked immunosorbent assay; ESR, erythrocytic sedimentation rate; HIV, human immunodeficiency virus; OCD, obsessive-compulsive disorder; PCN, penicillin; PCR, polymerase chain reaction; VDRL, Venereal Disease Research Laboratory.