Neuropsychiatric Masquerades

February 01, 2009 | Bipolar Disorder [1], Munchausen Syndrome [2], Sleep Deprivation [3], Panic Attacks [4], Mania [5], Forensic Psychiatry [6], Alcohol Abuse [7], Amnesia [8]
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Because numerous diseases— infectious, endocrinological, metabolic, and neurological, as well as connective-tissue disease— can induce psychiatric and/or behavioral symptoms, clinicians need to distinguish these neuropsychiatric masquerades from primary psychiatric disorders, warned José Maldonado, MD, the director of Stanford University's Psychosomatic Medicine Service.

Maldonado, associate professor of psychiatry and medicine at Stanford and chief of the medical and forensic psychiatry section at the Stanford University Medical Center, offered clinical guidance at the recent US Psychiatric and Mental Health Congress in San Diego.

While Maldonado explained that each entity has distinctive characteristics, there are several general clues that aid in identifying “organic” mental disorders (Table). In addition, Maldonado said, several prescription drugs (eg, corticosteroids, opioids, cancer chemotherapies, antiparkinsonian medications), substances of abuse (eg, cocaine, alcohol, phencyclidine [PCP]), and toxins (eg, heavy metals, paint, organophosphate insecticides) are linked with anxiety, mood disorders, and psychosis. Be suspicious if the patient is taking prescription drugs that have psychoactive effects, has a history of substance abuse, may have been exposed to toxins, or is taking multiple medications, he said.

“I happen to be the psychiatrist for the transplant teams at Stanford, and we have found that some transplant patients take over 20 different kinds of supplements that are not part of their therapy,” he said. “The other day, I . . . asked a patient to show me a list of his medications. He pulled out a bag of prescribed medications. I asked him if he took anything over-the-counter, and he brought out a bigger bag.”

Maldonado discussed more than 27 medical and neurological disorders that present with psychiatric symptoms, offered “pearls” for timely diagnosis, and discussed potential management and treatment strategies, some of which are described here.
Endocrine disorders

*Hypothyroidism* (myxedema madness) associated with rapid onset may clinically present with delirium and psychosis, according to Maldonado. *Myxedema madness* refers to the cognitive and psychotic symptoms, such as paranoid delusions, seen before the availability of effective treatment. In older adults, he added, hypothyroidism may present with dementia-like symptoms. Subclinical hypothyroidism can be virtually indistinguishable from depression and is often characterized by depression, memory loss, cognitive impairment, and fatigue. *Hyperthyroidism* (Graves disease) can present with anxiety, shortness of breath, sleep problems, and emotional lability. The disorder may be misdiagnosed as a mood or anxiety disorder, said Maldonado. Clinicians also have to think about CNS intoxication and consider whether the patient is using illicit drugs, such as cocaine.

In patients 65 years and older, hyperthyroidism can present with psychomotor retardation and cognitive deficits, often leading to a misdiagnosis of depression (known as apathetic hyperthyroidism). In patients with bipolar disorder, hyperthyroidism can lead to mania, he warned. *Pheochromocytoma*, a catecholamine-secreting tumor, can present with a number of symptoms. Primarily it mimics panic anxiety symptoms, including “paroxysmal attacks of anxiety,” according to Maldonado.

“These patients have many of the classic symptoms of anxiety disorder. But if you take a very good history, you will find that the anxiety attacks caused by pheochromocytoma do not meet the diagnostic criteria for panic attacks,” he said. “The diagnosis is not that difficult, although clinicians must have a high level of suspicion. Diagnostic tests include 24-hour urinary catecholamines and metanephrines; CT or T2- weighted MRI of the head, neck, and chest; or clonidine-suppression test. You can also massage the adrenal glands, which will produce a surge of catecholamines, and the patient will experience symptoms of a panic attack.”

The treatment of choice is to remove the tumor. But Maldonado cautioned that all the patients should be treated with b-blockers before surgery to prevent intraoperative hypertension.

“*Hyperparathyroidism* is often described as bones, stones, groans, and psychic moans,” Maldonado said. “Bones, because of the bone and joint changes or pain; stones, because a lot of patients develop kidney stones; groans, because of the GI symptoms; and psychic moans, because these patients are constantly tired and often develop restless legs syndrome.”

Overactivity of the parathyroid gland results in elevated parathyroid hormone levels causing hypercalcemia. Symptoms associated with hypercalcemia can include depression, decreased memory, loss of appetite, diminished concentration, and fatigue at lower levels. Symptoms may progress to confusion, psychosis, and delirium at very high levels. The treatment of choice is surgical removal.

*Hypoglycemia* early in its course may be confused with psychiatric disorders because some of the initial symptoms are fatigue and weight gain. Symptoms are variable and can also include decreased cognitive function, palpitations, sweating, anxiety, tremor, vomiting, delirium, or coma. When in doubt, give the patient a piece of candy or orange juice sweetened with sugar. In the emergency department, 50 mL of 50% dextrose is given for both treatment and diagnosis. Differential diagnosis of hypoglycemia includes alcohol use, fasting, insulinoma, and factitious hypoglycemia. Psychiatric symptoms (eg, psychosis or mood changes) occur in up to 80% of patients with insulinomas. Suspect an insulinoma, Maldonado said, if the symptoms are episodic and relieved by food intake.

**Metabolic disorders**

*Wilson disease* is an autosomal recessive disorder of copper metabolism, with decreased transport of copper from the liver into bile that leads to widespread accumulation of copper. This disease occurs in approximately 1 in 30,000 live births. Its usual presentation involves movement disorder, psychosis, and personality changes. About 35% of patients present with neurological symptoms, such as parkinsonianlike tremors and slurring of speech, and about 10% present with psychiatric problems ranging from subtle personality changes to overt depression, paranoia, and catatonia.
Diagnosis is often made clinically by the presence of Kayser-Fleischer rings adjacent to the cornea during a slitlamp examination, low levels (less than 20 mg/dL) of serum ceruloplasmin, elevated concentrations of copper in the cerebrospinal fluid, and hyperintensities in the basal ganglia and thalami shown by T2-weighted MRI of the brain.

Treatment is lifelong with various chelating agents, such as penicillamine (Cuprimine, Depen) or, alternatively, trientine (Syprine) or zinc. Maldonado warned that at the beginning of treatment, neurological symptoms can often worsen.

Porphyria is actually a group of autosomal dominant disorders that result from a partial deficiency of porphobilinogen deaminase, an enzyme required in the heme biosynthesis pathway. Acute intermittent porphyria can be associated with psychiatric symptoms (eg, psychosis) even when physical manifestations are not present, Maldonado explained. Early symptoms of acute porphyria can include minor behavioral changes; GI distress, such as abdominal pain, vomiting, and/or constipation; pain in the back and extremities; tachycardia; and hypertension. Neuropsychiatric symptoms that may accompany the acute attacks often include motor sensory neuropathy, seizures and confusion, as well as anxiety, apathy or depression, phobias, psychosis, agitation, mania-like states, and delirium.

To diagnose porphyria accompanied by predominantly neurological symptoms, Maldonado suggested a urine test to demonstrate elevated levels of porphobilinogen and delta-aminolevulinic acids, as well as other porphyrins. For diagnosis of porphyria with predominantly cutaneous symptoms, he recommended measurement of total plasma porphyrins.

INFECTIOUS DISEASES

“We could spend a whole month just talking about infectious diseases,” Maldonado said.

Lyme disease, for example, is often misdiagnosed. Lyme disease is caused by infection with the tick-borne spirochete *Borrelia burgdorferi*. There is a 3% chance of acquiring Lyme disease with each...
But it can take a few years before a diagnosis of Lyme disease is made, Maldonado said. Diagnosis involves exposure history, the characteristic *Erythema migrans* (rash), and 1 of 3 of the following: arthritis that waxes and wanes, neurological symptoms (eg, cranial or peripheral neuropathy, meningitis, encephalomyelitis, encephalitis), or cardiac conduction defects.

Maldonado referred to late stage Lyme disease, with a predominance of cognitive, psychiatric, and neurological symptoms, as *neuroborreliosis*. From a purely psychiatric perspective, the most common symptom of neuroborreliosis is depression. “I have seen many patients with Lyme disease and find it difficult to tell whether the depression is primary or secondary,” Maldonado said. Less common symptoms include panic attacks; transient paranoia, illusions, or hallucinations; anorexia; depersonalization; violent outbursts; obsessive-compulsive disorder; agitated mania; sensitivity to light or sound; and personality changes.

Several tests aid in diagnosis, including the serological studies with enzyme-linked immunosorbent assay, Western blot, or polymerase chain reaction (PCR) for borrelial DNA. One problem is that these serological studies may be equivocal, he said. A PET scan is helpful because it shows global or heterogeneous hypoperfusion; an MRI scan may show signs of demyelination.

If there is no CNS involvement, treatment is usually a long course of doxycycline (Vibramycin and others), amoxicillin (Amoxil and others), or cefuroxime (Ceftin). With CNS involvement, the regimen is 4 to 6 weeks of IV ceftriaxone (Rocephin) or cefotaxime (Claforan).

**Herpes infection.** More than 1 in 5 adult Americans have genital herpes, and 50% to 80% of American adults have oral herpes, according to the American Social Health Association. Herpes simplex virus (HSV) is the etiological agent for *herpes simplex encephalitis* (HSE); up to 70% of untreated cases of HSE are fatal.

HSE, Maldonado said, is characterized by an abrupt onset of fever, personality changes, and headaches, followed by cognitive changes and focal neurological signs (such as aphasia). Neuropsychiatric symptoms include an initial presentation with hallucinations, memory loss or behavioral disturbances, progression to refractory seizures, coma, and possibly death. Survivors may exhibit postencephalitic symptoms of amnesia, aphasia, and Klver-Bucy syndrome or dementia. Leukocytosis, moderate protein elevation, and a normal or depressed glucose level in cerebrospinal fluid are some diagnostic clues. PCR analysis will detect HSV DNA, and a brain MRI can detect inflammation.

HSE is treated with the antivirals acyclovir (Zovirax) and vidarabine (Vira-A).

**Connective tissue disease**

*Systemic lupus erythematosus* (SLE) is characterized by recurrent episodes of destructive inflammation of several organs including the skin, joints, kidneys, blood vessels, and CNS. Psychosis, cognitive defects, and dementia have all been described as psychiatric manifestations of SLE.

“About 5% of patients suffering from lupus cerebritis have psychosis, usually within the first 2 years of having the disease,” said Maldonado. “But physicians need to distinguish between steroid psychosis and SLE psychosis.”

Treatment for SLE psychiatric symptoms can include corticosteroids, cyclophosphamide (Cytoxan) and, possibly, antipsychotics.

**Delirium**

Maldonado, who has focused on delirium in his research, emphasized that it is the most common neurobehavioral disorder among medically ill patients in general hospitals. Its incidence ranges from about 15% in the general medicine wards, to 40% in surgical wards, to up to 80% in the ICUs. A single cause for delirium is seldom identified, he said, but the most common risk factors include older age, baseline cognitive functioning, male gender, the use of exogenous agents with high anticholinergic load (usually associated with illicit or prescribed substances), immobility or physical restraints, sleep deprivation, and the severity of the underlying medical illness process.

Understanding, preventing, and treating delirium is important because of the severe consequences it carries greater morbidity and mortality; longer hospitalizations, higher incidence of placement in extended care facilities, and increased cost of care; and permanent cognitive impairment or development of other psychiatric disorders, such as posttraumatic stress disorder, he said.

“The condition is often missed or misdiagnosed by general medical practitioners.” Maldonado added that “it is an area where psychiatrists can have a great impact.”

Extensive information about delirium can be found in 2 articles by Maldonado in the October 2008 issue of Critical Care Clinics. One article proposes a pathoetiological model of delirium, and the
second discusses the characteristics, diagnosis, and treatment of delirium. The bottom line, cautions Maldonado: keep in mind that medical or neurological illnesses may be contributing factors to a patient’s neuropsychiatric symptoms.

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