A curious case of depression

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Mr. Z, age 61, has a history of bipolar I disorder and presents with worsening depression, fatigue, thrombocytopenia, and a rash. What is exacerbating his symptoms?

Mr. Z, age 61, is referred by his primary care clinician to the hospital's medical service with increasing depressive symptoms and non-pruritic rash. He has a history of bipolar I disorder for >30 years. When the primary care physician evaluated Mr. Z, his vitals were normal, but blood work revealed mild anemia and thrombocytopenia of 34 x10^3/µL, which prompted referral to the hospital. During admission, the psychiatric consultation service is called to evaluate Mr. Z's depressive symptoms.

Mr. Z reports having chronic sleep problems and feeling cold and tired, shivering at times, but has no pain. He says he's worried because he feels severely depressed, worthless, and hopeless, but denies suicidal ideation and psychosis. Mr. Z says he started experiencing increasingly depressed mood, anhedonia, insomnia, fatigue, poor appetite, and concentration 2 months ago. At that time his outpatient psychiatrist started Mr. Z on risperidone, 6 mg/d, and divalproex, 1,500 mg at bedtime because of emerging mood symptoms, after he was off medication for 7 months. Mr. Z attributed his worsened mood symptoms to being overwhelmed by several psychosocial stressors, including going through a complicated divorce, financial problems, and homelessness after being evicted from his apartment.

A review of Mr. Z's psychiatric history reveals several remote hospitalizations—the last was 7 years ago—for escalated manic symptoms after he stopped taking his medication. He denies past suicide attempts. Mr. Z says he is compliant with his current medication regimen—risperidone, 6 mg/d, and divalproex, 1,500 mg at bedtime. He denies illicit drug use and says he drinks "a couple of beers, mostly on weekends." Family history is positive for depression and bipolar II disorder.

His medical history is significant for hypothyroidism after goiter removal 6 years ago, for which he takes levothyroxine, 150 mcg/d, and a sports injury-related splenectomy in childhood. He reports no allergies. Vital signs at the time of admission are temperature, 99.1°F; pulse, 98 beats per minute; respiration, 16 breaths per minute; blood pressure, 123/73 mm/Hg; and oxygen saturation, 97%.

During the interview, Mr. Z presents with tired facies and exhibits psychomotor retardation. He has to force himself to stay engaged in the evaluation and maintain eye contact. His speech is clear, regular, and soft. Mr. Z says he is "very depressed"; his affect is constricted, almost flat, stable, and consistent with depressed mood. His thought process is linear and somewhat concrete and his thought

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How would you handle this case?

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Clinical Point

Rapid valproate titration can mimic neurovegetative symptoms and cause dose-dependent thrombocytopenia and rash

Table 1

Differential diagnosis in patients presenting with mood changes

Cerebrovascular disease
Degenerative disorders (Parkinson's disease, Huntington's disease, Wilson's disease)
Demyelinating disorders (multiple sclerosis, amyotrophic lateral sclerosis, lipid storage disease)
Endocrine disorders (Addison's disease, Cushing's disease, hyperthyroidism, hypothyroidism, hyperparathyroidism, pituitary dysfunction)
Epilepsy
Infectious diseases
Immune diseases
Metabolic encephalopathy
Neoplasm
Nutritional deficits (thiamine, niacin, vitamin B12)
Primary psychiatric disorders (mood disorders, dementia, sleep disorders)
Substance use
Toxins/medications
Traumatic brain injury

Source: Reference 1

content is notable for hopelessness, although Mr. Z continues to deny suicidal or homicidal ideations. No hallucinations or apparent delusions are noted. Insight and judgment are fair. Mr. Z understands his current mental state; however, he displays some lack of knowledge regarding his current hospitalization. Cognition is intact.

What is the possible explanation for Mr. Z's clinical presentation?

a) reaction to stressors such as his divorce, financial problems, and homelessness
b) an endocrine disorder
c) pharmacologic effect
d) infection
e) all of the above

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The authors' observations

The differential diagnosis in patients presenting with mood changes is extensive (***Table 1***)[1] and in Mr. Z's case includes several precipitating and perpetuating factors. Mr. Z presents with severe depressive symptoms and meets DSM-IV-TR criteria for a major depressive episode (MDE). This presentation is not typical of his bipolar I disorder because Mr. Z has never experienced an MDE and usually presents with escalating hypomanic/manic symptoms in the context of medication nonadherence. Nevertheless, Mr. Z has several risk factors for severe depression, including a family psychiatric history, multiple enduring social stressors and life crises, and medical conditions.

In the general population, the lifetime risk for developing depression is 8% to 17%.[2] The risk of developing a mood disorder increases significantly if a first-degree relative is diagnosed with a mood disorder; the relative risk is 10.3 for bipolar disorder and 3.2 for depression.[3] Additionally, Mr. Z is going through a complicated divorce, has financial problems, and is homeless, all of which could trigger an MDE. Furthermore, hypothyroidism shares many symptoms of depression, including fatigue, lethargy, anhedonia, cold intolerance, and low mood; mental status changes frequently are the initial presentation of thyroid problems.[4] Physicians started Mr. Z on a new medication regimen (risperidone and divalproex) to control mood instability, which coincided with symptom onset. Atypical antipsychotics have been reported to precipitate depressive symptoms; their side effect profile includes extrapyramidal effects, such as flat affect, which can be mistaken for depression.[5] Rapid valproate titration can mimic neurovegetative symptoms of depression and cause dose-dependent thrombocytopenia and rash, which could explain his initial presentation.[6] Finally, Mr. Z's history of traumatic splenectomy, change in mental status, and thrombocytopenia suggest an infectious etiology.

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Table 2

Potential infectious causes of chronic encephalopathy

Type of infection	Organism/disease
Mycobacterial	*Mycobacterium tuberculosis*
Spirochetal	*Treponema pallidum* (syphilis), *Borrelia burgdorferi* (Lyme disease), *Leptospira*
Bacterial	*Brucella*, *Listeria*, *Nocardia*, *Actinomyces israelii*, Whipple's disease
Viral	HIV/AIDS, cytomegalovirus, varicella zoster virus, herpes simplex virus, enterovirus
Fungal	Histoplasmosis, coccidiosis, *sporothrix*, *Blastomyces*, *Cryptococcus*
Parasitic	Toxoplasmosis, *taenia solium* (cysticercosis), *Schistosoma*, *Acanthamoeba*

AIDS: acquired immunodeficiency syndrome; HIV: human immunodeficiency virus

Source: Reference 8

Possible infectious causes

The increased prevalence of immune suppression due to human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) or from therapeutic modalities such as cancer therapy or splenectomy has led to an increased number of chronic CNS infections, manifesting with an array of neuropsychiatric symptoms and nonspecific physiological reactions.[1,7] Mr. Z complains of a 2-month period of worsening depression that could suggest an infectious process with an insidious onset. Some infectious agents that can cause chronic CNS infection and encephalopathy are presented in ***Table 2***.[8] HIV, tuberculosis, syphilis, Lyme disease, and herpes simplex virus are becoming more prevalent and can present with neuropsychiatric symptoms.[1] For example, in addition to thrombocytopenia and low-grade fever, patients with HIV may exhibit a broad range of neuropsychiatric symptoms such as cognitive problems, impaired executive and motor functioning, sleep disturbance, and anxiety. These patients frequently present with low mood and neurovegetative symptoms of depression.[7] Similarly, the same tick responsible for Lyme disease infection can transmit other infectious agents that can cause thrombocytopenia, including *Babesia*, *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*, and human *Ewingii ehrlichiosis*.

How would you manage Mr. Z?

a) discontinue divalproex and decrease risperidone
b) start antidepressants to treat depressive symptoms
c) order blood tests to check for infectious agents
d) refer Mr. Z for psychotherapy to help him manage his life stressors

The authors' observations

Diagnosis of a mood change, particularly an MDE, is clinical, based on careful psychiatric evaluation using standardized criteria rather than a specific lab test. However, some laboratory studies (***Table 3, page 74***)[1] are useful in differentiating medical illnesses that may present with depression. Mr. Z's presentation warrants investigating these tests. His history of traumatic splenectomy and night sweats suggests an infection. The team's initial recommendations include laboratory tests, discontinuing divalproex because it may be causing thrombocytopenia, and decreasing risperidone to 2 mg/d to improve his fatigue and possibly developed extrapyramidal symptoms.

continued

Clinical Point

HIV, tuberculosis, syphilis, Lyme disease, and herpes simplex virus can present with neuropsychiatric symptoms

Clinical Point

Clinical features of Lyme disease stages frequently overlap and some patients in later stages do not have prior signs or symptoms

Table 3

Differentiating medical illnesses that may mimic depression

Laboratory tests
CBC, thyroid-stimulating hormone, antinuclear antibody, erythrocyte sedimentation rate, vitamin B12, rapid plasma reagin, HIV test, electrolytes and calcium levels and renal function test, liver function tests, blood alcohol, blood, and urine toxicology screen, ABG, Lyme antibody test (ELISA), dexamethasone suppression test (Cushing's disease), cosyntropin stimulation test (Addison's disease)
Imaging studies
CT scan or MRI of the brain
Other tests
EEG
Procedures
Lumbar puncture for VDRL, Lyme antibody, cell count, chemistry, and protein electrophoresis

ABG: arterial blood gases; CBC: complete blood count; EEG: electroencephalogram; ELISA: enzyme-linked immunosorbent assay; HIV: human immunodeficiency virus; VDRL: venereal disease research laboratory

Source: Reference 1

TREATMENT Cause revealed

Mr. Z develops a persistent fever of 102°F with continuous profuse sweating and a hypotensive episode. Blood work reveals mild anemia, thrombocytopenia, and increased coagulation parameters with high D-dimer and low fibrinogen, consistent with diagnosis of disseminated intravascular coagulation (DIC) secondary to infectious etiology. Thyroid and HIV tests are negative. After further evaluation, Mr. Z remembers that 4 months earlier he removed several ticks from his legs after hunting; he also remembers experiencing shivering and night sweats several weeks before he was hospitalized. His blood smear is positive for babesiosis and further testing confirms positive Lyme antibodies. Mr. Z is started on aggressive hemodynamic stabilization and a pathogen-tailored course of antibiotics for several weeks. This results in improvement and discharge home in a stable condition. His depression and fatigue improve but do not fully remit by the time he is discharged.

Which psychiatric symptoms would you anticipate in patients with Lyme disease?

a) fatigue
b) sleep disruptions
c) decreased concentration
d) depressed mood
e) all of the above

The authors' observations

Lyme disease is one of the fastest-growing infectious diseases in the United States.[9] The prevalence of positive Lyme antibodies is 30% higher in psychiatric populations than the general population.[10] Lyme disease is transmitted by deer tick bite, often undetected, that is infected with spirochete *Borrelia burgdorferi*. To be infectious, ticks need to be attached to the skin for 24 to 48 hours,[11,12] although individual cases have reported transmission in <24 hours. The clinical manifestations of Lyme disease can be divided into 3 phases:

- early localized phase, characterized by the distinctive skin lesion erythema migrans with or without constitutional symptoms
- early disseminated phase, characterized by multiple erythema migrans lesions and neurologic and/or cardiac findings
- late or chronic disease associated with intermittent/persistent arthritis and/or neurologic problems.[11,13]

The clinical features of each stage frequently overlap and some patients in a later stage of Lyme disease do not have prior signs or symptoms of the disease. Because it is a multisystem disease, Lyme disease can attack the CNS in the form of neuroborreliosis, a clinical diagnosis, without involving other systems, and its neuropsychiatric manifestations can resemble neurosyphilis because both organisms are spirochetes.[11,13,14] CNS disorders have been found in up to 40% of Lyme disease cases.[11] In neuroborreliosis, cognitive problems usually predominate; however, neuroborreliosis can mimic multiple brain diseases presenting with various neurologic and psychiatric symptoms (***Table***

4)[14,15] and can present at any time after the tick bite. Furthermore neuroborreliosis is difficult to diagnose because symptoms may remain dormant and emerge after several years.[11,13,14] *Borrelia burgdorferi* is challenging to isolate and grow in the lab, and enzyme-linked immunosorbent assay (ELISA) testing for antibodies is highly specific but not very sensitive,[16] frequently giving false negative results. Western blot confirms the diagnosis.

Mr. Z's presentation also reflects co-infection with babesiosis. *Babesia* is malaria-like protozoa diagnosed by blood smear that can cause a fatal illness in immunocompromised patients. The clinical picture varies from mild symptoms such as night sweats, chills, arthralgias, and anorexia with thrombocytopenia to severe and potentially fatal outcomes in immunocompromised patients, including DIC, acute renal failure, sepsis, congestive heart failure, and myocardial infarction.[11] Risk factors for the severest forms of babesiosis are age >50, co-infection with Lyme disease, and splenectomy,[11] all of which were present in Mr. Z. Co-infected patients experience fatigue, headache, anorexia, and emotional lability more frequently than those with Lyme disease alone.[12]

Treatment options

Treatment of Lyme disease/neuroborreliosis is complex. The mainstay approach is antibiotics. Despite adequate treatment, many patients experience continued impairment, including chronic pain, fatigue, and cognitive and psychiatric symptoms.[11,14] There is some evidence *Borrelia burgdorferi* can persist and re-emerge after adequate treatment.[14,17] The National Institute of Health sponsored several clinical trials of prolonged antibiotic treatment for chronic Lyme disease. Some results suggested improvement in fatigue and cognitive function, although these results were not sustained.[18]

Table 4

Late-stage neuropsychiatric symptoms of Lyme disease

Cognitive problems, memory problems, forgetfulness, slowing of thought processing, dysfunction in visuospatial orientation, dyslexia
Depression
Mood swings
Psychosis
Violent behavior/irritability
OCD
Anxiety
Panic attacks
Sleep disorders
Seizures
ADHD-like symptoms
Autism-like behavior
Chronic fatigue syndrome
Fibromyalgia

ADHD: attention-deficit/hyperactivity disorder; OCD: obsessive-compulsive disorder

Source: References 14,15

There is a strong link between mental illness and increased prevalence of positive Lyme disease antibodies.[10] Several studies report increased risk of infection during psychological stress that may be related to an altered immune system response.[19] Evidence suggests that *Borrelia burgdorferi* can alter immune system response, making T cells more reactive not only to *Borrelia burgdorferi* antigens but also to host antigens,[20] creating autoimmune inflammatory reactions that could explain chronic neuropsychiatric symptoms. It appears Lyme disease antigens can mimic certain autoantigens (for example, in the thyroid gland).[21] Whether there is a role for autoimmune therapy in treating chronic symptoms needs to be investigated.

Once Lyme disease is diagnosed, educating patients and families becomes an important part of treatment because many patients report feeling stigmatized by the diagnosis. Referral to a Lyme disease support group may be beneficial. Patients

Clinical Point

Despite treatment, many Lyme disease patients have continued impairment, including pain, fatigue, and cognitive symptoms

Related Resource

- Centers for Disease Control and Prevention. Lyme disease: Resources for clinicians. www.cdc.gov/lyme/healthcare/clinicians.html.

Drug Brand Names

Divalproex sodium • Depakote
Levothyroxine • Levoxyl, Synthroid
Risperidone • Risperdal

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Clinical Point

Many Lyme disease patients report feeling stigmatized, making educating patients and family an important part of treatment

with neuropsychiatric symptoms that persist after antibiotic treatment should be offered symptom-based treatment, including medications and therapy.

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Bottom Line

Psychiatric symptoms such as depression and fatigue may be the only manifestations of Lyme disease. Lyme encephalopathy should be in the differential diagnosis of patients with atypical or complex presentation of mood disorders and/or acute mental status changes. Careful interviewing and history-taking that includes screening for deer tick exposure are essential.