Uncooperative and manic

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After refusing medications and hemodialysis, Ms. Z, age 69, develops mania. She experiences mild anxiety and has multiple medical comorbidities. What's causing her mania?

CASE New-onset mania

Ms. Z, age 69, is admitted to our hospital's medical unit after developing manic symptoms. Her medical history includes hemodialysis-dependent chronic kidney disease, Parkinson's disease stabilized by carbidopa/levodopa, 75/300 mg/d, for 4 years, diet-controlled type 2 diabetes mellitus, hypertension, hyperlipidemia, myelodysplasia, and acid reflux. She experiences mild anxiety, which has been stable for many years with escitalopram, 10 mg/d, but has no history of alcohol or drug abuse and no family history of psychiatric illness.

The staff at her assisted living facility reports that 8 days ago Ms. Z was mildly irritable and argumentative regarding her medications and 7 days ago began to refuse all medications. Six days ago she refused dialysis, reportedly because she was angry at the staff. One day later, the staff noticed Ms. Z had developed manic symptoms, including decreased need for sleep (only 2 hours a night), talkativeness, counting things and spelling words rapidly out loud, and making explicit drawings of men. Ms. Z refused her next 2 dialysis treatments and her manic symptoms worsened. She explained that all her medical problems had been "cured." She inaccurately exclaimed that she can urinate, even though she is anuric, and that she can walk after not having done so for 5 years.

During our interview, Ms. Z is disheveled and exhibits pressured speech, often interrupting the interviewer. Her affect is euphoric and expansive. She perseverates on patenting her cures for diabetes and Parkinson's disease, endorses hypersexuality, and denies hallucinations. Folstein Mini-Mental State Exam score is 18/28; however, Ms. Z refuses to participate in elements of cognitive testing, including writing a sentence, drawing pentagons, or drawing a clock, all of which would reveal her tremor. We note no disorientation or waxing and waning of attention or consciousness. She is fully oriented to person, place, time, and purpose and can perform serial 7s and spell a word backwards.

What is the most likely cause of Ms. Z's presentation?

a) bipolar mania
b) mood disorder due to a general medical condition (Parkinson's disease)
c) mood disorder due to a general medical condition (uremia)
d) substance-induced mood disorder
e) delirium

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continued

How would you handle this case?

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Table 1

Criteria for mood disorder due to a general medical condition

A. A prominent and persistent disturbance in mood predominates in the clinical picture and is characterized by either (or both) of the following: (1) depressed mood or markedly diminished interest or pleasure in all, or almost all, activities (2) elevated, expansive, or irritable mood
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition
C. The disturbance is not better accounted for by another mental disorder
D. The disturbance does not occur exclusively during the course of a delirium
E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Source: Reference 1

Clinical Point

In delirium, we would expect EEG to show diffuse slowing of background rhythm, which we did not see with Ms. Z

The authors' observations

A number of factors suggest that Ms. Z's manic symptoms likely are caused by a medical problem (***Table 1***).[1] She has no family history and only minimal personal history of psychiatric illness, and new-onset bipolar disorder in a 69-year-old woman is unusual.[2] Given Ms. Z's acute change in mental status and numerous medical problems, we consider delirium. Because Ms. Z does not exhibit disorientation or waxing and waning of attention or consciousness, we feel delirium is unlikely to be the primary diagnosis.

What further workup would you request?

a) urinalysis
b) head CT or MRI
c) electroencephalography (EEG)
d) neurology consultation

EVALUATION Clues to the cause

Physical exam reveals stable vital signs, and resting tremor and mild cogwheel rigidity in her right upper extremity consistent with Parkinson's disease. Laboratory results show elevated blood urea nitrogen (65 mg/dL) and creatinine (8 mg/dL) and stably low white cell count (2.9/µL) and platelets (118x10^3/µL), which are consistent with her known myelodysplasia. Results for urinalysis, B12, folate, thyroid-stimulating hormone, electrolytes, glucose, liver function, antinuclear antibodies, and rapid plasma reagin are unremarkable. Ms. Z's elevated blood urea nitrogen and creatinine are expected because she recently refused dialysis. We consider that uremia could be causing her manic symptoms; however, with only 2 case reports of uremia-induced mania in the literature over the past century, we want to rule out other potential causes.[3,4]

A CT of Ms. Z's brain is normal. The neurology service performs an EEG and results show mild disorganization with a predominantly posterior rhythm of 8 to 9 Hz symmetrically, occasional periods of slowing, and no epileptiform activity or evidence of encephalopathy; these findings are consistent with end-stage renal disease.

The authors' observations

Although mood disorder due to a general medical condition—in this case, mania secondary to uremia—was our primary consideration, at this point we could not rule out subclinical delirium. In delirium, we would expect EEG to show diffuse slowing of background rhythm, which we did not see with Ms. Z. However, occasional periods of slowing indicate that delirium was a possible factor.

Parkinson's disease is known to be a rare predisposing factor for mania—possi-

bly related to potential manicogenic properties of dopaminergic medications[5]—but this would not explain new-onset mania in the context of uremia in a patient whose carbidopa/levodopa dose had been stable for several years. It is possible that Ms. Z's refusal of dialysis could have led to build-up of carbidopa/levodopa in her blood, thereby contributing to mania; however, when she began feeling irritable, she refused several of her medications, including carbidopa/levodopa. Therefore, it is unlikely that carbidopa/levodopa accumulated to toxic levels.

We carefully evaluated Ms. Z's complete medication list to determine if other drugs could be contributing factors. She has been taking escitalopram for anxiety for several years. Although Ms. Z had no personal or family history of bipolar disorder and no past hypomania or agitation associated with this medication, we discontinue escitalopram in case it was contributing to her manic symptoms. Ms. Z also receives amlodipine, 5 mg/d for hypertension; atorvastatin, 20 mg/d, for hyperlipidemia; pantoprazole, 40 mg/d, for acid reflux; metoprolol, 100 mg/d, for hypertension; aspirin, 81 mg/d, for cardioprotection; and fish oil, 2000 mg/d, for cardioprotection. We do not feel that any of these medications significantly contribute to her current state.

TREATMENT Restarting dialysis

We start Ms. Z on olanzapine, 5 mg/d, for manic symptoms 1 day after admission, and resume dialysis treatments 1 day later. Because of concerns that olanzapine could worsen her myelodysplasia, we switch to aripiprazole, titrating up to 30 mg/d, 4 days later. After 2 dialysis treatments, her manic symptoms begin to resolve.

The authors' observations

A number of factors suggest that uremia likely is causing Ms. Z's manic symptoms. Her symptoms suddenly developed shortly after her first missed dialysis treatment, but gradually resolved after re-initiating dialysis. It is possible that antipsychotics relieved her manic symptoms, but this does not detract from the factors that make a causal relationship between uremia and mania likely.

Manic symptoms have been reported to be precipitated by a variety of medical problems, including metabolic disturbances, infections such as human immunodeficiency virus brain infection, neurologic disorders, brain neoplasms, or traumatic brain injuries (***Table 2***).[6,7] End-stage renal disease frequently is associated with psychiatric manifestations—including depression, psychosis, delirium, and dementia—but mania is not a typical presentation. It is possible that this condition occurs more often but is not recognized.

Table 2

Common causes of secondary mania

Metabolic/endocrine disturbances (hyperthyroidism, hyperadrenalism)
Infections (HIV)
Neurologic disorders (cerebrovascular accident, multiple sclerosis, Parkinson's disease, epilepsy, Huntington's disease)
Brain neoplasms
Traumatic brain injuries
Medications (anabolic steroids, antidepressants, corticosteroids, dextromethorphan, dopamine agonists, hypericum, isoniazid, stimulants, ephedrine, zidovudine)
Substance abuse (cocaine, amphetamines)

HIV: human immunodeficiency virus

Source: References 6,7

Kidney disease and psychotropics

We considered the effect of dialysis on psychotropics when selecting pharmacotherapy for Ms. Z's manic symptoms. Haloperidol is not renally cleared so no dosage adjustment is necessary;[8] however, this potent dopamine D2-blocker could

Clinical Point

End-stage renal disease frequently is associated with psychiatric manifestations, but mania is not a typical presentation

Related Resource

- Arora M, Daughton J. Mania in the medically ill. Curr Psychiatry Rep. 2007;9(3):232-235.

Drug Brand Names

Amlodipine • Norvasc
Aripiprazole • Abilify
Atorvastatin • Lipitor
Carbamazepine • Tegretol
Carbidopa/levodopa • Sinemet
Escitalopram • Lexapro
Haloperidol • Haldol
Isoniazid • Nydrazid
Lithium • Eskalith, Lithobid
Metoprolol • Lopressor
Olanzapine • Zyprexa
Pantoprazole • Protonix
Quetiapine • Seroquel
Valproic acid • Depakote
Zidovudine • Retrovir

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

Olanzapine, quetiapine, and aripiprazole do not require dosage adjustments for dialysis patients

have worsened Ms. Z's parkinsonism. Lithium is contraindicated in acute renal failure. Valproic acid clearance is reduced in renal failure, but because it is cleared by hemodialysis, dosage adjustment is not recommended for dialysis patients.[8] However, Ms. Z's myelodysplasia is a contraindication for valproic acid as well as carbamazepine. With atypical antipsychotics as our primary options, we noted that olanzapine, quetiapine, or aripiprazole do not require dosage adjustments for dialysis patients.[8,9] Of these, we eventually chose aripiprazole because we felt that it was least likely to exacerbate Ms. Z's myelodysplasia.[10]

How uremia might cause mania

The pathophysiology of uremia-induced mania remains speculative. Possible factors include:

- Chronic renal failure can cause an elevation in plasma free tryptophan, a serotonin (5-HT) precursor.[11] Postmortem examination of brains of patients who died in uremic coma show elevated 5-HT.[12] Moreover, cerebrospinal fluid of patients with chronic renal failure has shown increased 5-hydroxyindoleacetic acid, the major 5-HT metabolite.[13] Increased 5-HT could cause mania in some uremic patients, similar to how serotonergic medications can precipitate mania in some patients.
- Circulating ß-endorphin levels are increased in renal failure.[14] ß-endorphins increase animal locomotor activity, which is the basis of an animal model of mania.[15,16] Therefore, uremia-induced mania could be partly related to elevated ß-endorphin levels.

This case demonstrates that mania could be a psychiatric manifestation of end-stage renal disease. Clinicians should be aware of this possibility, and further study should examine underlying pathophysiologic changes in uremia and other secondary causes of mania that might lead to such a mood state.

OUTCOME Lasting improvement

At discharge 17 days after admission, Ms. Z is back to her baseline mental state. Her aripiprazole dose is tapered to 20 mg/d with no return of manic symptoms. After 10 weeks, aripiprazole is discontinued, with no recurrence of mania.

Bottom Line

Suspect underlying medical etiologies of acute, new-onset psychiatric symptoms, including mania, in older patients, particularly if they have no personal or family history of mental illness. Such patients should receive careful medical workup, with primary psychiatric disorders being diagnoses of exclusion. Although rare, uremia can lead to a first lifetime episode of mania.

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