From the Johns Hopkins Hospital

Delirium Presenting as Mania in a Patient With End-Stage COPD

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Case Presentation

"Ms. M," a 65-year-old Caucasian woman with end-stage chronic obstructive pulmonary disease related to smoking and α-1-antitrypsin MS phenotype, developed an abrupt onset of agitation and confusion and was admitted to the medical service of a local hospital. Until then, her only psychiatric treatment was for anxiety, which had been treated with escitalopram for the previous 5 months. Shortly after a dosage adjustment for increased anxiety symptoms (from 10 mg/day to 20 mg/day), Ms. M became acutely restless, anxious, and cognitively disorganized. She was found to be hypercarbic but not hypoxic on her normal dosage of supplemental oxygen (see Table 1 for details). The patient's medications on admission included escitalopram, prednisone, esomeprazole, diltiazem, tiotropium, and fluticasone. EEG showed mild diffuse slowing. A serum sodium level of 126 mEq/L (reference range, 135–145 mEq/L) suggested escitalopram-associated syndrome of inappropriate secretion of antidiuretic hormone, so the drug was discontinued, the hyponatremia was corrected, and the patient was discharged in 4 days, much improved. Her prednisone dosage was unchanged.

Five days later, Ms. M exhibited unusually intense cleaning behavior at home, pressured speech, flight of ideas, and paranoid delusions. She was returned to the emergency department, from which she immediately fled, attempting to run into traffic before being coaxed back inside. She was sedated with intramuscular injections of haloperidol and lorazepam and admitted to the medicine department (admission 2 in Table 1). Her electrolyte levels were normal and her blood gases essentially unchanged. The consulting psychiatrist noted the patient's anxiety and compulsive behavior and prescribed sertraline, buspirone, and alprazolam. Ms. M's pulmonologist tapered her prednisone dosage by 25%. Ms. M calmed without further incident and was discharged 3 days later.

Within 2 weeks, she again rapidly decompensated; she was observed to be speaking feverishly on the telephone without anyone on the other end, and she stayed awake at night, writing nonsensically. She began to insist falsely that her husband was a verbally abusive alcoholic and became irate when challenged. On admission to a local psychiatric unit (admission 3), she was noted to have elated mood, pressured speech, flight of ideas, decreased need for sleep (3 hours nightly), delusions, and psychomotor agitation. Sertraline was discontinued (as a possible cause of her manic symptoms), olanzapine was introduced, and lithium was added without significant benefit. Results from a battery of tests, including lumbar puncture, heavy metal screen, HIV, antinuclear antibodies, Lyme disease, rapid plasma reagin, erythrocyte sedimentation rate, and levels of ceruloplasmin, C-reactive protein, and B_{12}, were all normal. EEG showed slow waves, but was read as "normal." A brain MRI revealed no interval change.

The psychiatric treatment team, noting the "normal" EEG and continuing mood lability, agitation, and paranoia, recommended ECT for presumed psychotic mania. Examinations several times during the hospitalization found Ms. M to have been oriented, although memory impairment was noted on admission and again on the day before initiation of ECT, when her attending psychiatrist documented impairment in concentration as well as in remote and recent memory. Ms. M then received three bifrontal ECT treatments, with fleeting improvement of agitation but no return to baseline. She was discharged home with 24-hour private-duty nursing support. Her medication regimen included olanzapine, alprazolam, and a reduced dosage of prednisone. She was removed from the lung transplant waiting list because of her psychiatric admission. Three additional outpatient bifrontal ECT treatments, a retrial of lithium (serum level, 0.5 mmol/L), and continued olanzapine failed to stem worsening disorganization.

Two months after the first appearance of agitation and confusion, Ms. M traveled out of state to be admitted to the mood disorders unit at Johns Hopkins Hospital (admission 4). On arrival, she had an unsteady gait and was minimally cooperative. She grabbed at random objects, attempted to remove her clothing, and attempted to get into the shower while dressed. Her speech was slow, dysarthric, and tangential. Her mood alternated between irritable and cheerful. She accused her husband of being an alcoholic. She was oriented only to person, scoring 17 (out of 30) on the Mini-Mental State Examination (MMSE). Her medications on admission included olanzapine, prednisone, alprazolam as needed, diltiazem, omeprazole, fluticasone, and ipratropium.

EEG revealed bilateral posterior slowing. Blood gas levels indicated well-compensated chronic hypercarbia ($Paco_2$ now up to 70 mmHg). The patient's lithium level was not assessed, as lithium had been discontinued several days before admission. An extensive delirium workup for serum markers of metabolic, nutritional, autoimmune, endocrine,

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paraneoplastic, and infectious etiologies was negative aside from mild hyperammonemia (serum ammonia level, 31–68 μg/dL; reference, <35 μg/dL) consistent with α-1 antitrypsin deficiency. Lumbar puncture revealed normal cytopathology; CSF gram stain, culture, and viral polymerase chain reaction tests were all negative; and a 14-3-3 protein test for Creutzfeldt-Jakob disease was negative. The patient was diagnosed with delirium from multiple likely sources, including metabolic insults, severe hypercarbia, prolonged steroid exposure, benzodiazepine intoxication, and recent ECT.

Prednisone was tapered to 1 mg/day, alprazolam and olanzapine were discontinued, and low-dosage risperidone was started. Although initially the patient was agitated, attempting to strike nursing staff and repeatedly removing her nasal cannula, over the next several days she had periods of lucidity, intact memory, and normalized gait. The agitation and delusions resolved, and the patient became increasingly accepting of the nasal cannula. Her MMSE score was 30 on discharge 2 weeks later. Her family judged her to be nearly back to normal at that time.

Ms. M remained psychiatrically stable for 2 weeks after discharge, but she was then hospitalized in the intensive care unit for *Pseudomonas* pneumonia (admission 5). Throughout, she remained frankly delirious, intubated, and restrained, with insomnia and occasional agitation managed with risperidone and quetiapine as prescribed by the psychiatric consultation service. Once medically stabilized, she was discharged with a tracheostomy to a rehabilitation facility near her home. Her mental state returned to normal, and she was decannulated and returned home. With a letter of support from the attending psychiatrist at Johns Hopkins Hospital attesting to the likely physiologic cause for her psychosis, she was placed back on the waiting list for a lung transplant.

Within a month, she was selected for transplant; however, she simultaneously suffered an abrupt relapse of anxiety, agitation, paranoia, and bizarre behavior. She was admitted locally to a medical unit (admission 6), and no new factors were identified that might have caused delirium. Discontinuation of prednisone led to no improvement. Mindful of the potential for medication-related delirium, her treatment team prescribed only conservative dosages of risperidone and quetiapine, but she continued to be agitated, labile, and confused. She was transferred to Johns Hopkins Hospital 3 weeks later, this time to the psychogeriatric unit. In contrast to her original presentation to Johns Hopkins, she was now hypervigilant, with rapid and intermittently unintelligible speech and marked grandiosity. She was uncooperative but fully oriented. Also in contrast to her initial presentation, she could not be encouraged by staff to keep her nasal cannula in place, responding instead by hitting, kicking, and biting, and thus required four-point restraints for the initial 2 weeks of her stay.

A workup for delirium revealed bilateral symmetric slowing and the absence of a posterior basic rhythm on EEG. There were no new significant changes on other laboratory study results. The patient refused a brain MRI. She was not taking corticosteroids on admission.

Quetiapine at dosages up to 800 mg/day produced minimal tranquilization, and risperidone at dosages up to 9 mg/day led to significant but partial improvement. The patient gradually became less grandiose, belligerent, and hypervigilant, and she was safely removed from restraints. Three weeks into her stay, she became disoriented and had acute respiratory decompensation, evidently triggered by a malfunctioning continuous positive airway pressure device, that required a 3-day transfer to the intensive care unit, where she received prednisone, an antibiotic, and pulmonary support (but not intubation). During the patient's brief stay in the intensive care unit, her code status was modified to "do not resuscitate/do not intubate," as the medical team believed her prognosis was dire. However, the family requested that her status be restored to full code before her return to the psychiatric unit.

On transfer back to the psychiatric unit, Ms. M was again fully oriented and lucid, though euphoric, hyperverbal, grandiose, and readily agitated. Lithium was then added to her medication regimen, and the remaining manic symptoms resolved. Ms. M regained insight and exhibited a sense of humor about her prior delusional ideas. Retreat from high-dosage neuroleptics progressed smoothly, and she thus was discharged on low dosages of risperidone, quetiapine, and lithium (lithium serum level, 0.3–0.4 mmol/L).

The absence of an identified cause for delirium is often mistakenly used as a rationale for concluding that the patient's problem is primarily "functional" as opposed to "organic."

Three months after discharge, Ms. M was able to undergo successful lung transplantation. Under her psychiatrist's supervision, she gradually discontinued all psychotropic medications over the course of about a year. As of 30 months after surgery, she remains in stable physical and psychiatric health and recalls very little about her episodes of delirium and mania.

Discussion

The case illustrates the important diagnostic point that a manic state secondary to a medical condition can persist even when other clinical signs of delirium have faded. It also demonstrates some of the intricate clinical dilemmas that can arise in the management of agitated, medically unstable patients.

Ms. M's illness illustrates the overlap of manic symptomatology and physiologic impairment of brain activity that has led to hybrid concepts such as "secondary mania," which has been applied to a manic syndrome that occurred for the first time in a medically compromised individual (1), and "hyperactive delirium," which is a common presentation for delirium in many clinical settings (2–4). Many etiologies have been linked to delirium (5, 6), and Ms. M had been exposed to several, including hypercarbia, prednisone, hyponatremia, hyperammonemia, benzodiazepines,

TABLE 1. Summary of Admissions and Treatment[a]

Date, Service, and Location[b]	Clinical Status	EEG Findings	Other Data[c]	Daily Doses of Psychotropic Medications[d] (mg)	Daily Dose of Prednisone (mg)
Jan. 16–20: medicine, local hospital (admission 1)	Altered mental status	Mild diffuse background slowing; excessive beta activity	Na: 123 → 135 mEq/L; brain MRI: mild generalized cortical atrophy; arterial pH: 7.37; $Paco_2$: 55 mmHg	Escitalopram: 20 → 0	10
Jan. 25–28: medicine, local hospital (admission 2)	Pressured speech, flight of ideas, paranoia		Arterial pH: 7.38; $Paco_2$: 58 mmHg	Sertraline: 0 → 50; buspirone: 0 → 15	10 → 7.5
Feb. 8–29: psychiatry, local hospital (admission 3)	Involuntary admission; ECT, bifrontal, 3 treatments	Slow waves but "normal"	Brain MRI: no interval change	Sertraline: 50 → 0; buspirone: 15 → 30 → 0; olanzapine: 0 → 10; lithium: 0 → 300	7.5 → 2.5
Feb. 29–March 11; home	Relapse of confusion and disorganization; outpatient ECT, bifrontal, 3 treatments		Lithium level: 0.5 mmol/L	Lithium: 300 → 600 → 0; olanzapine: 10 → 7.5	2.5 → 2.0
March 11–28: psychiatry, JHH (admission 4)	Delirious	Bilateral posterior slowing	MMSE score: on admission, 17; range during admission, 7–28; arterial pH: 7.35; $Paco_2$: 69 mmHg	Olanzapine: 7.5 → 0; risperidone: 0 → 3 → 1.5	2.0 → 0
April 13–May 11: ICU, JHH (admission 5)	Intubated for pneumonia, ICU delirium		Arterial pH/$Paco_2$: on admission, 7.59/42 mmHg; while intubated, 7.39/64 mmHg; at discharge, 7.36/74 mmHg	Trazodone: 0 → 25; risperidone: 1.5 → 3; quetiapine: 0 → 6.25	50 (1 dose); 0 → 5 → 20
July 24–Aug. 13: medicine, local hospital (admission 6)	Worsening agitation			Quetiapine: 6.25 → 100	20 → 0 (taper)
Aug. 13–30: psychiatry JHH (transfer)	Manic	Bilateral symmetric slowing, absent posterior basic rhythm	Arterial pH: 7.37; $Paco_2$: 72 mmHg	Quetiapine: 100 → 300; risperidone: 4 → 7; lithium: 0 → 100	0
Aug. 30–Sept. 2: ICU, JHH	Biphasic positive airway pressure		Arterial pH/$Paco_2$: on admission, 7.32/87 mmHg; at discharge, 7.36/74 mmHg	No medication changes	30 (1 dose)
Sept. 2–30: psychiatry, JHH	Normal mental state at discharge	Normal	Prolactin 133–141 μg/L; MMSE score: 28 at discharge; lithium level: 0.4 mmol/L	Quetiapine: 200 → 25; risperidone: 7 → 9 → 1.5; lithium: 100 → 300	40 (1 dose)
Sept. 30–Oct. 10; home	Stable, then lung transplantation			Risperidone: 1.5 → 0; lithium: 300 → 0	

[a] ICU=intensive care unit; MMSE=Mini-Mental State Examination; JHH=Johns Hopkins Hospital.
[b] The dates have been altered to preserve anonymity but are accurate relative to one another.
[c] Where arterial blood results are provided, we have included pH, as a sensitive indicator of respiratory decompensation, and $Paco_2$, as it trended upward independently of periods of acute respiratory decompensation. Normal arterial pH=7.35–7.45; normal $Paco_2$=35–45 mmHg. We have omitted oxygen levels, as they added little useful information.
[d] "As-needed" prescriptions for benzodiazepines have been omitted.

and the anticholinergic effects of other somatic drugs. However, aside from the hypercarbia and mild hyperammonemia (which were present even when the patient was perfectly calm and lucid), none of these factors was present continuously from the beginning to the end of her illness.

Over the entire course of illness, Ms. M experienced a series of exacerbations of delirium. For this oxygen-dependent patient, any behavioral change that interfered with adherence to her nasal cannula became a critical problem, as the consequence of inadequate oxygenation was inevitably an exacerbation of her delirium. Furthermore, any new clinical problem that exacerbated the delirium also amplified the management problem posed by her agitation.

Appropriate treatment demanded close attention to the clinical assessment of the patient's mental state. On first presentation to Johns Hopkins Hospital, Ms. M was disoriented and disorganized but responsive to redirection. The initial strategy thus focused on removing potentially deliriogenic factors—minimizing psychoactive medications and ensuring nasal cannula adherence. When this approach was repeated later, it proved inadequate to control the patient's combative, delusional, but fully oriented state; safe management required external restraints, and the patient's agitation and manic ideation resolved only with a combination of lithium and two neuroleptics.

Diagnostic dependence on an identifiable medical cause or on test results proved to be misleading at times. In the diagnosis of delirium, EEG can be helpful to confirm the clinical diagnosis, but it neither proves nor disproves delirium in uncertain cases (7, 8). The absence of an identified cause for delirium is often mistakenly used as a rationale for concluding that the patient's problem is primarily "functional" as opposed to "organic." As indicated by Ms. M's full recovery and stable mental condition after transplantation, chronic hypercarbia probably contributed significantly to her manic presentation of delirium (9), and lung transplantation was thus the definitive treatment for her mental condition.

Conclusions

This case illustrates the need for flexibility in the treatment approach to a patient with differing degrees and presentations of a delirium with manic symptoms. A thorough evaluation to identify and correct physical disorders that can perturb the mental state—in this case, transient hyponatremia, pneumonia, polypharmacy, corticosteroid therapy, and hypoxemia—proved necessary but not sufficient to restore the patient to adequate mental health to make her eligible for lung transplantation. Judicious but assertive psychopharmacologic intervention, close collaboration with nursing staff, and ready availability of acute medical intervention all combined to stabilize the patient's condition sufficiently that lung transplantation proved the definitive psychiatric intervention.

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Clinical Guidance: Delirium With Manic Symptoms in End-Stage COPD

The case of a delirious woman with chronic obstructive pulmonary disease who needed a lung transplant required collaboration between psychiatric and pulmonary teams. Wilkinson et al. report that her manic symptoms and agitation caused her removal from transplant eligibility. Likely causes for the delirium included metabolic insults, severe hypercarbia because of her inability to comply with respiratory therapy, prolonged steroid exposure, benzodiazepine intoxication, and recent ECT, administered in attempts to reverse her delirium. After transfer to the teams at Johns Hopkins, her prednisone was tapered to 1 mg/day. She was treated with low-dose risperidone, which was eventually supplemented by moderate doses of quetiapine and lithium (serum level, 0.3 mmol/L). After a several months' relapsing and remitting course for both the delirium and lung disease, her mood and pulmonary status eventually stabilized and she underwent successful lung transplantation.