After 3 months, she's still 'mad'

Leonard Lachover, MD

Ms. A thinks doctors and 'the Mafia' are out to get her. Why is she so violent, paranoid, and delusional despite months of aggressive antipsychotic treatment?

HISTORY 'They want to kill me'

Police and security agents arrest Ms. A, age 64, at a metropolitan airport. She is extremely agitated and behaving bizarrely, yelling that "the Mafia" is trying to kill her. She has spent 3 days hiding in area hotels, fleeing her "assailants."

Police arrange Ms. A's return home; under court order, she is hospitalized in a psychiatric facility. She is diagnosed with paranoid schizophrenia and receives IM haloperidol, 2 mg bid, but shows minimal improvement after 2 ½ weeks. Her psychotic symptoms improve slightly after the psychiatrist switches her to risperidone, 2 mg bid, but she still cannot function normally. Three weeks after admission, she is transferred to a nursing home for long-term care. She continues risperidone but remains paranoid and delusional.

Three months later, Ms. A is rehospitalized. She is anxious, delusional, confused, and hallucinating at admission. The patient is verbally and physically combative, fearful that medical staff will harm her. She is too violent to be examined, but staff notice that her skin appears thickened, her eyes puffy, and her hair coarse. Her voice sounds low and raspy.

I speak with Ms. A's son, who reports that before his mother's arrest he found her in the kitchen wielding a knife, exclaiming she wanted to kill herself. He says she heard a "whoosh" or "ringing" in her right ear while a male voice in her left ear told her, "End it, end it."

Ms. A is severely obese (weight 325 lbs, body mass index 49 kg/m^2). Blood pressure is 140/90 mm Hg, and she is taking captopril, 50 mg bid, for hypertension. Pulse rate and temperature are normal.

How would you treat Ms. A after 2 failed antipsychotic trials?

a) electroconvulsive therapy (ECT)
b) clozapine
c) combination antipsychotic/mood stabilizer therapy
d) reconsider the diagnosis

Dr. Lachover's observations

Ms. A's hallucinatory experiences are atypical, and her psychotic symptoms show little response after 2 months of aggressive inpatient treatment. Three months after discharge, she is rehospitalized in a florid paranoid psychotic state.

The patient's weight poses an additional obstacle. I avoided second-generation antipsychotics (SGAs) that can cause weight gain, such as clozapine or olanzapine. I tried the SGA risperidone after IM haloperidol, a first-generation antipsychotic, produced minimal response.

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Table 1

Ms. A's thyroid panel values

Component	Ms. A's readings	Normal values
Serum cholesterol	310 mg/dL	100 to 199 mg/dL
TSH (thyrotropin)	31.07 mIU/L	0.25 to 4.30 mIU/L
Free T4	0.34 ng/dL	0.80 to 1.80 ng/dL
Total T4 (serum thyroxine)	1.5 µg/dL	4.6 to 12 µg/dL
Total T3 (serum triiodothyronine)	67 ng/dL	70 to 180 ng/dL

Ms. A's physical symptoms (thickened skin, coarse hair, puffiness under her eyes, and vocal raspiness) suggest an underlying organic process that might be causing her psychosis.

TESTING Telling results

I order laboratory and other tests to check for an underlying organic disorder:

- Brain MRI is normal, as are CBC, renal and liver function, and serum copper, ceruloplasmin, vitamin B_{12}, and heavy metal levels.
- Slit lamp eye exam reveals no Kayser-Fleischer ring, which would have indicated Wilson's disease.
- EEG shows a diffuse, nonspecific, abnormal pattern of slowing and decreased amplitude, suggesting diffuse cerebral dysfunction.
- ECG shows sinus bradycardia and a significantly prolonged corrected QT (QTc) interval, indicating delayed ventricular repolarization.
- Thyroid panel is abnormal with markedly elevated thyrotropin (31.07 mIU/L).

I consult an internist, who diagnoses hypothyroidism based on Ms. A's thyroid panel (***Table 1***). An endocrinologist also is consulted. Ms. A is started on levothyroxine, 0.025 mg/d, and continues risperidone, 2 mg bid, to address her paranoia and delusions.

Across 3 weeks, Ms. A's delusional perceptions and hallucination intensity decrease, and her reality testing and socialization skills improve. She is discharged, after which the internist and I see her weekly to monitor thyroid function and psychiatric symptoms, respectively. Thyroid function gradually returns to normal over 4 to 6 months, and she is maintained on levothyroxine, 0.025 mg/d. Her weight gradually decreases over 12 months to 229 lbs.

Six months after discharge, Ms. A is notably more adept at activities of daily living. Mental status exam shows progressively improved reality testing and decreased paranoia. She is more active, and her mood and affect have brightened. Risperidone is stopped 10 months after discharge, and she has not been rehospitalized for psychiatric problems.

Dr. Lachover's observations

Erroneously diagnosed with paranoid schizophrenia, Ms. A endured 2 extended hospitalizations. Her psychosis and mental state—both of which improved with thyroid replacement therapy—appear to have been a psychiatric manifestation of severe hypothyroidism, or "myxedema madness" (***Box, page 86***).[1-3]

Myxedema prevalence in the general public has been reported at 0.5% to 18%. It is roughly 10 times more common in women than in men,[4] and 5% to 15% of patients with myxedema might develop signs of psychosis.[4] Myxedema-induced psychosis usually occurs during middle age but has been reported between ages 18 and 73. Prevalence increases with age.[4]

Recognizing 'myxedema madness'

Detecting and treating myxedema in patients with treatment-resistant psychosis can resolve psychiatric and medical symptoms and restore quality of life. Left untreated, it can impair cognitive function and cause

Clinical Point

Lack of response to 2 months of aggressive antipsychotic treatment could suggest a medical cause for psychosis

lethargy, dysarthria, myopathy, neuropathy, status epilepticus, and coma.[5-7]

Psychiatric manifestations of severe hypothyroidism vary greatly, and a pre-existing psychotic disorder can worsen the presentation. Confusion, disorientation, persecutory delusions, hallucinations, and violent episodes are common symptoms.[8] The patient may resist medical examination, fearing her life is in danger or the physician is conspiring to harm her.

Myxedema can impair perception and intellectual functioning,[9] and acute mania has been reported in some cases.[10] Increasing delirium reduces integration of perceptual input, leading to misidentification and disorientation. Cognitive functioning may be impaired, and abnormal thyroid hormone levels might delay event-related brain potential.[11]

Physical signs also can be telling. The patient might show general psychomotor retardation and slowed speech. The tongue might be swollen, the voice hoarse and croaking. Hair is often coarse and brittle, with hair loss along the sides of the eyebrows. Body temperature often dips below normal.[4]

Patients with hypothyroidism usually gain weight, leading to subcutaneous depositions of fat that frequently appear as a "buffalo-hump" or periorbital edema known as "myxedema facies."[12] Because myxedema increases risk of heart disease, elevated cholesterol, and hypertension, immediate treatment is mandatory for severely obese patients such as Ms. A.

When should Ms. A have been tested for hypothyroidism?

a) At presentation
b) After one failed antipsychotic trial
c) After two failed antipsychotic trials

Clinical Point

Order medical tests for all patients with psychotic symptoms—particularly if onset occurs after age 40

Dr. Lachover's observations

Detecting Ms. A's hypothyroidism early could have prevented needless hospitalizations and failed treatment. Order a baseline thyroid panel for every patient who presents with psychotic symptoms or depression, which is the primary affective disturbance seen in myxedema.

Serum cholesterol >200 mg/dL, anemia and hypertension, basal metabolic rate ≤20% of normal levels, triiodothyronine (T3) <70 ng/dL, total thyroxine (T4) <4.5 µg/dL, or thyrotropin (TSH) >4.5 mIU/L suggest myxedema (***Table 2, page 89***).

Box

What causes psychosis, depression in myxedema?

Researchers have proposed many potential causes for the psychotic and depressive symptoms seen in myxedema.

Psychotic symptoms. Tonks[1] has attributed psychosis in myxedema to decreases in cerebral oxygenation and glucose metabolism, resulting in a relative cerebral hypoxia. Among patients with myxedema, Sheinberg et al[2] reported markedly reduced cardiac output and found that:

- cerebral blood flow was reduced 38%
- oxygen and glucose absorption were decreased approximately 30%
- cerebrovascular resistance was notably increased.

Depressive symptoms. Catecholamine deficiency at the neuronal receptor sites might cause depression in hypothyroidism. Evidence suggests that thyroid hormone influences catecholamine function at the neuronal level.[3]

Monoamine oxidase, which is increased in myxedema, has also been implicated. This enzyme might lead to depression by helping to break down catecholamines at the neuronal axon-dendrite levels.[3]

How would you handle this case?

Visit www.**currentpsychiatry**.com to input your answers and compare them with those of your colleagues

continued on page 89

continued from page 86

Table 2

Is it myxedema? Check the lab findings

Component	Values that suggest myxedema
Serum cholesterol	>200 mg/dL
Free T4	<0.8 ng/dL
Total T4 (serum thyroxine)	<4.5 µg/dL
Total T3 (serum triiodothyronine)	<70 ng/dL
TSH (thyrotropin)	>4.5 mIU/L
EEG	Diffuse slowing
EKG	Prolonged QTc interval

Diffuse slowing of background activity is the most common EEG change found in myxedema.[13] ECG might show slow, regular sinus rhythm or bradycardia, low voltage, prolonged QTc interval, and flattened T waves.[14] Prolonged QRS complexes on ECG indicate delayed ventricular repolarization.[11,15] Torsades de pointes, the potentially fatal ventricular tachycardia, can result from a prolonged QTc interval in rare myxedema cases.[16]

Treating 2 sets of symptoms

Prescribe concomitant dessicated thyroid and low-dose antipsychotics over 4 to 6 months to treat both the thyroid dysfunction and psychosis. Because weight gain is common in myxedema, choose an antipsychotic that carries a relatively low risk of weight gain, such as risperidone, 2 mg bid, or aripiprazole, 5 to 10 mg/d.

Many patients reach euthyroidism and their psychosis improves gradually but notably over weeks or months after starting thyroid hormone replacement. Psychosis could recur if desiccated thyroid is stopped; restarting it will improve the patient's mental state.[17] Recovery takes about 3 months on average.[4]

Continue the SGA until delusion perception is gone and reality testing improves, then taper the medication until all psychotic symptoms have abated. Monitor thyroid function monthly.

For patients with myxedema-induced depression, supplement thyroid hormone replacement with a selective serotonin reuptake inhibitor such as sertraline at regular starting dosages.

What other undiagnosed medical problems can cause treatment-resistant psychosis?

a) Alzheimer's disease
b) electrolyte imbalance
c) Wilson's disease
d) anticholinergic syndrome
e) any of the above

Dr. Lachover's observations

Consider contributing medical illness in any patient with psychosis, particularly with psychotic symptom onset after age 40 and lack of response to weeks of adequate antipsychotic therapy.

A meticulous search to rule out medical disorders in all patients with psychosis and/or depression is essential to planning treatment. Testing is especially urgent for elderly patients, as multiple medical comorbidities or medication side effects can mask hypothyroidism's signs and symptoms and delay diagnosis.[18]

Check complete blood count, electrolytes, thyroid panel, urinalysis, urine drug screen, blood urea nitrogen, and creatinine to rule out an underlying metabolic or endocrinologic cause for psychosis. Watch for signs of anticholinergic syndrome during physical examination.

If any of the above results suggest a medical problem, test for the following as clinical suspicion warrants:

- serum copper/ceruloplasmin and liver function to rule out Wilson's disease, a genetic disorder that causes copper to accumulate in the liver and brain
- systemic lupus erythematosus
- lead, magnesium, mercury, or manganese to rule out metal poisoning.

continued

Clinical Point

Disorientation, persecutory delusions, hallucinations, and violent episodes are common myxedema symptoms

Related Resources

- Cronin AJ. *The Citadel*. Boston: Little, Brown & Co.;1937:399.
- Asher R. Myxoedamatous madness. *BMJ* 1949;2:555-62.

Drug Brand Names

Aripiprazole • Abilify
Captopril • Capoten
Clozapine • Clozaril
Haloperidol • Haldol
Levothyroxine • Synthroid
Olanzapine • Zyprexa
Risperidone • Risperdal

Disclosures

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

Bottom Line

Recognizing hypothyroidism early as a cause of psychosis can prevent needless treatment and improve outcome. Order a thyroid panel and other laboratory tests for all patients who present with psychotic or depressive symptoms. If thyroid dysfunction is causing psychosis, treat both problems simultaneously.

Order additional blood testing to check for vitamin B_{12} deficiency, brain MRI to rule out Alzheimer's or subcortical dementia, EEG to check for an infectious or malignant disorder or for cerebral dysfunction, or ECG to rule out a metabolic or degenerative disorder or electrolyte imbalance.

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