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GRAND ROUNDS

Recent onset of confusion, limited mobility, and disturbed sleep-wake cycle

This elderly woman had received treatment the week before for pneumonia and paranoid behavior. How would you proceed with her care?

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A 66-year-old woman has a 6-day history of confusion, reduced food intake, and limited mobility. Although the patient has no recent history of fever, rigors, cough, shortness of breath, chest pain, urinary frequency, or burning micturition, she does report a disturbed sleep-wake cycle. A week before, the patient was discharged from a local hospital where she was treated for community-acquired pneumonia with moxifloxacin 400 mg daily, and for paranoia with haloperidol 2 mg twice a day and mirtazapine 15 mg daily. Her family reports escalating confusion and tremor of her hands over the past week.

Q How would you focus your initial assessment?

A

Additional medical history

- The patient's medical history is significant for deep venous thrombosis, coronary artery disease, hypertension, chronic obstructive pulmonary disease (COPD), atrial fibrillation, major depressive disorder, and agoraphobia.
- In addition to the haloperidol and mirtazapine she was recently prescribed, the patient is taking paroxetine 20 mg daily, furosemide 40 mg twice daily, domperidone 10 mg 4 times daily, amlodipine 10 mg daily, atorvastatin 20 mg daily, warfarin 2 mg daily, trazodone 50 mg daily, oxycodone 5 mg twice daily, meloxicam 15 mg daily, tramadol 37.5 mg 3 times a day, and imipramine 25 mg daily.

Physical examination

- The patient is oriented to person, but not to time or place.
- Oral temperature is 37.3˚C.
- Pulse rate is 97 beats/min.
- Respiratory rate is 28 breaths/min.
- Blood pressure is 118/83 mm Hg.
- Cardiovascular and abdominal systems are unremarkable.
- Neurological examination demonstrates increased tone and tremor (resting and postural) in arms and legs, as well as brisk reflexes in the upper limbs but not in the lower limbs.

Laboratory results

- Blood and serum levels are normal for hemoglobin, platelets, sodium, potassium, and phosphorus.
- Several blood or serum values are abnormal:
  - White blood cell count, 16.1×10^9 cells/L (normal: 4.1-10.0)
  - Serum urea, 16.8 mmol/L (normal: 3.0-7.1)

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- Creatinine, 187 µmol/L (normal: 60-130)
- Chloride, 96 mmol/L (normal: 98-110)
- Anion gap, 25 mmol/L (normal: 10-20)
- Corrected calcium, 1.54 mmol/L (normal: 2.14-2.66)
- Magnesium, 0.54 mmol/L (normal: 0.70-1.10)
- Albumin, 33 g/L (normal: 35-50)
- Creatine kinase (CK), 3435 U/L (normal: 30-135)
- Urinalysis shows traces of ketones and is positive for blood.
- International normalized ratio is 6.0 (normal: < 1).

Radiographic findings

- A chest x-ray shows extensive ill-defined interstitial markings in the right upper lobe, suggestive of pneumonia.
- Computed tomography shows hypodense areas of the subcortical white matter of the cerebral hemispheres in the brain, indicative of age-related ischemic demyelination.

Onset of serotonin syndrome is usually rapid, often occurring within 24 hours of starting or changing medications.

Q What is your presumptive diagnosis?

A

A case of serotonin syndrome?

The most likely diagnosis is serotonin syndrome induced by adding mirtazapine to the patient's ongoing paroxetine regimen. In fact, the patient was already at risk from the combination of drugs she had been taking.

Serotonin (5-HT) is a neurotransmitter with a high prevalence in the midline raphe nuclei, located in the brain stem from the midbrain to the medulla.[1] These neurons play a role in sleep-wakefulness cycles, mood, emotions, eating behavior, and thermoregulation.[2] Overstimulation of postsynaptic 5-HT_{2A} receptors on these neurons leads to the development of serotonin syndrome.

The syndrome encompasses a triad of systems: mental-status changes, including agitation, confusion, and hypervigilance; autonomic hyperactivity, such as tachycardia, fever, shivering, mydriasis, hyperreflexia, hyperactive bowel sounds, sialorrhea, and clonus; and neuromuscular abnormalities, such as heightened rigidity, tremor, myoclonus, and hypertonicity.[3] Laboratory findings reflective of serotonin syndrome include elevated CK levels associated with rhabdomyolysis, metabolic acidosis, elevated levels of serum aminotransferase and creatinine, as well as low platelet and fibrinogen levels and high fibrin degradation products due to disseminated intravascular coagulation. If left untreated, the syndrome can result in coma and even death.

Symptomatic onset of serotonin syndrome is usually rapid and often occurs within 24 hours of starting or changing medications. A number of agents have been implicated as potential causes of serotonin syndrome (**TABLE**). The most common causes are increasing the dose of a selective serotonin reuptake inhibitor (SSRI) or adding a serotonergic drug to an existing SSRI regimen. With therapeutic doses of SSRIs, adding any drug that inhibits the cytochrome P450 2D6 or 3A4 isoenzymes will also result in higher serum levels of serotonin and increase the likelihood of serotonin syndrome. For example, the CYP3A4 inhibitors erythromycin and linezolid have been known to induce serotonin syndrome in some patients who are taking SSRIs.[4,5]

Q What other possible disorders might you want to rule out?

A

Three diagnoses are possible alternatives for serotonin syndrome.

Anticholinergic syndrome shares with serotonin syndrome the features of delirium, hypertension, tachycardia, hyperthermia, and mydriasis. However, features distinguishing anticholinergic syndrome are absence of clonus, normal reflexes, absence of bowel sounds, dry mucosa, and dry, hot skin.[3] Symptoms often appear within 12 hours of overdose of anticholinergic medication.[3]

Neuroleptic malignant syndrome, after exposure to dopamine antagonists, develops more slowly than serotonin syndrome,

over 1 to 3 days. Hypertension, tachycardia, hyperthermia, sialorrhea, and diaphoresis are features of both syndromes. However, "lead pipe-like" rigidity, hypoactive reflexes, and bradykinesia point to neuroleptic malignant syndrome.[3]

Malignant hyperthermia causes hypertonicity, hyperthermia, hypertension, tachycardia, agitation, and metabolic acidosis, as does serotonin syndrome. In malignant hyperthermia, the skin could be mottled with areas of bright red flushing and cyanosis. Its rigidity is rigor mortis-like, and reflexes are absent or hypoactive. Symptoms can appear within 30 minutes to 24 hours after exposure to inhalational anesthetic agents.[3]

The key differentiators for serotonin syndrome are hyperreflexia and clonus.[6] Reflexes are normal in anticholinergic syndrome, and are absent or hypoactive in neuroleptic malignant syndrome and malignant hyperthermia. Clonus is not a feature of anticholinergic syndrome, neuroleptic malignant syndrome, or malignant hyperthermia.

TABLE
Medications that can cause serotonin syndrome[3]

Serotonin reuptake inhibitors
Serotonin-norepinephrine reuptake inhibitors (eg, venlafaxine)
Tricyclic antidepressants
Monoamine oxidase inhibitors
Sibutramine
Dextromethorphan
Valproate
Opioids (eg, meperidine, fentanyl, tramadol)
Triptans (eg, sumatriptan, zolmitriptan)
Serotonin releaser (eg, methylenedioxymethamphetamine [MDMDA, "Ecstasy"])
Serotonin precursor (eg, tryptophan)
St. John's wort

CONTINUED

Bromocriptine and dantrolene, used to treat neuroleptic malignant syndrome, are contraindicated in serotonin syndrome.

Q How would you treat this patient?

A

Remove the precipitating agent

The first step in treating serotonin syndrome is to withdraw the offending agent—often a medication that was recently added or whose dosage was recently increased. After this step, symptoms usually resolve within 24 hours. But they may persist for days if the drug involved has a long half-life. Administering a $5HT_{2A}$ antagonist, such as cyproheptadine, may be useful when more aggressive treatment is required. Cyproheptadine, a histamine 1 receptor antagonist, is given orally (or crushed and administered through a nasogastric tube) at an initial dose of 12 mg, and subsequently at 4 to 8 mg every 6 hours.[7] Alternatively, another $5HT_{2A}$ antagonist, chlorpromazine, can be given 50 to 100 mg intravenously.[8]

Ensure that the patient receives supportive care. Administration of intravenous (IV) fluids and correction of electrolyte and metabolic abnormalities are the mainstays of supportive treatment.

Benzodiazepine may need to be administered if the patient exhibits uncontrolled agitation. Hyperthermia (usually due to muscle hyperactivity) typically resolves itself and does not require antibiotics or antipyretics. However, severe cases of serotonin syndrome with uncontrolled hyperthermia may require sedating the patient, inducing neuromuscular paralysis, and initiating orotracheal intubation and ventilation.

Take precautions. Bromocriptine and dantrolene, which are used to treat neuroleptic malignant syndrome, are contraindicated in serotonin syndrome and may worsen serotonergic signs.[9] Extreme caution is therefore warranted with patients who may be taking both serotonergic and antipsychotic medications, or in cases when the diagnosis is in doubt.

The patient's outcome

After our initial assessment, we discontinued all antidepressant and antipsychotic medications, administered IV fluids, and monitored the patient's electrolytes. Treatment with lorazepam and cyproheptadine led to improvement. Her confusion and tremors subsided, and her CK values normalized within 48 hours. After a psychiatric consultation, we began slow-release venlafaxine at a dose of 37.5 mg/d. At discharge, we arranged a follow-up appointment for the patient in the community. **JFP**

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