A SELF-TEST ON A CLINICAL CASE

CME CREDIT *LEARNING OBJECTIVE:* Readers will evaluate and investigate the possible causes of new-onset seizure

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A 50-year-old woman with new-onset seizure

A 50-year-old woman presented to the emergency department after a witnessed loss of consciousness and seizurelike activity. She reported that she had been sitting outside her home, drinking coffee in the morning, but became very lightheaded when she went back into her house. At that time she felt could not focus and had a sense of impending doom. She sat down in a chair and her symptoms worsened.

According to her family, her eyes rolled back and she became rigid. The family helped her to the floor. Her body then made jerking movements that lasted for about 1 minute. She regained consciousness but was very confused for about 10 minutes until emergency medical services personnel arrived. She had no recollection of passing out. She said nothing like this had ever happened to her before.

On arrival in the emergency department, she complained of generalized headache and muscle soreness. She said the headache had been present for 1 week and was constant and dull. There were no aggravating or alleviating factors associated with the headache, and she denied fever, chills, nausea, numbness, tingling, incontinence, tongue biting, tremor, poor balance, ringing in ears, speech difficulty, or weakness.

Medical history: Multiple problems, medications

The patient's medical history included depression, hypertension, anxiety, osteoarthritis, and asthma. She was allergic to penicillin. She had undergone carpal tunnel surgery on her right hand 5 years previously. She was perimenopausal with no children.

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She denied using illicit drugs. She said she had smoked a half pack of cigarettes per day for more than 10 years and was a current smoker but was actively trying to quit. She said she occasionally used alcohol but had not consumed any alcohol in the last 2 weeks.

She had no history of central nervous system infection. She did report an episode of head trauma in grade school when a portable basketball hoop fell, striking her on the top of the head and causing her to briefly lose consciousness, but she did not seek medical attention.

She had no family history of seizure or neurologic disease.

Her current medications included atenolol, naproxen, gabapentin, venlafaxine, zolpidem, lorazepam, bupropion, and meloxicam. The bupropion and lorazepam had been prescribed recently for her anxiety. She reported that she had been given only 10 tablets of lorazepam and had taken the last tablet 48 hours previously. She had been taking the bupropion for 7 days. She reported an increase in stress lately and had been taking zolpidem due to an altered sleep pattern.

After prodromal symptoms, she lost consciousness for about 1 minute, with jerking

PHYSICAL EXAMINATION, INITIAL TESTS

On examination, the patient did not appear to be in acute distress. Her blood pressure was 107/22 mm Hg, pulse 100 beats per minute, respiratory rate 16 breaths per minute, temperature 37.1°C (98.8°F), and oxygen saturation 98% on room air.

Examination of her head, eyes, mouth, and neck were unremarkable. Cardiovascular, pulmonary, and abdominal examinations were normal. She had no neurologic deficits and was fully alert and oriented. She had no visible injuries.

Blood and urine samples were obtained about 15 minutes after her arrival to the emergency department. Results showed:

- Glucose 73 mg/dL (reference range 74–99)
- Sodium 142 mmol/L (136–144)
- Blood urea nitrogen 12 mg/dL (7–21)
- Creatinine 0.95 mg/dL (0.58–0.96)
- Chloride 97 mmol/L (97–105)
- Carbon dioxide (bicarbonate) 16 mmol/L (22–30)
- Prolactin 50.9 ng/mL (4.5–26.8)
- Anion gap 29 mmol/L (9–18)
- Ethanol undetectable
- White blood cell count 11.03 × 10^9/L (3.70–11.00)
- Creatine kinase 89 U/L (30–220)
- Urinalysis normal, specific gravity 1.010 (1.005–1.030), no detectable ketones, and no crystals seen on microscopic evaluation.

Electrocardiography showed normal sinus rhythm with no ectopy and no ST-segment changes. Chest radiography was negative for any acute process.

The patient was transferred to the 23-hour observation unit in stable condition for further evaluation, monitoring, and management.

Her symptoms strongly suggest a new-onset tonic-clonic or grand mal seizure

SIGNS AND SYMPTOMS OF SEIZURE

1 What findings are consistent with seizure?

- ☐ Jerking movements
- ☐ Confusion following the event
- ☐ Tongue-biting
- ☐ Focal motor weakness
- ☐ Urinary incontinence
- ☐ Aura before the event

All of the above findings are consistent with seizure.

The first consideration in evaluating a patient who presents with a possible seizure is whether the patient's recollections of the event—and those of the witnesses—are consistent with the symptoms of seizure.[1]

In generalized tonic-clonic or grand mal seizure, the patient may experience an aura or subjective sensations before the onset. These vary greatly among patients.[2] There may be an initial vocalization at the onset of the seizure, such as crying out or unintelligible speech. The patient's eyes may roll back in the head. This is followed by loss of muscle tone, and if the patient is standing, he or she may fall to the ground. The patient becomes unresponsive and may go into respiratory arrest. There is tonic stiffening of the limbs and body, followed by clonic movements typically lasting 1 to 2 minutes, or sometimes longer.[1,3,4] The patient will then relax and experience a period of unconsciousness or confusion (postictal state).

Urinary incontinence and tongue-biting strongly suggest seizure activity, and turning the head to one side and posturing may also be seen.[3,5] After the event, the patient may report headache, generalized muscle soreness, exhaustion, or periods of transient focal weakness, also known as Todd paralysis.[2,5]

Our patient had aura-like symptoms at the outset. She felt very lightheaded, had difficulty focusing, and felt a sense of impending doom. She did not make any vocalizations at the onset, but her eyes did roll backward and she became rigid (tonic). She then lost muscle tone and became unresponsive. Her family had to help her to the floor. Jerking (clonic) movements were witnessed.

She regained consciousness but was described as being confused (postictal) for 10 minutes. Additionally, she denied ever having had symptoms like this previously. On arrival in the emergency department, she reported generalized headache and muscle soreness, but no tongue-biting or urinary incontinence. Her event did not last for more than 1 to 2 minutes according to her family.

Her symptoms strongly suggest new-onset tonic-clonic or grand mal seizure, though this is not completely certain.

LABORATORY FINDINGS IN SEIZURES

2 What laboratory results are consistent with seizure?

- ☐ Prolactin elevation
- ☐ Anion gap acidosis
- ☐ Leukocytosis

As noted above, the patient had an elevated prolactin level and elevated anion gap. Both of these findings can be used, with caution, in evaluating seizure activity.

Prolactin testing is controversial

Prolactin testing in diagnosing seizure activity is controversial. The exact mechanism of prolactin release in seizures is not fully understood. Generalized tonic-clonic seizures and complex partial seizures have both been shown to elevate prolactin. Prolactin levels after these types of seizures should rise within 30 minutes of the event and normalize 1 hour later.[6]

However, other events and conditions that mimic seizure have been shown to cause a rise in prolactin; these include syncope, transient ischemic attack, cardiac dysrhythmia, migraine, and other epilepsy-like variants. This effect has not been adequately studied. Therefore, an elevated prolactin level alone cannot diagnose or exclude seizure.[7]

For the prolactin level to be helpful, the blood sample must be drawn within 10 to 20 minutes after a possible seizure. Even if the prolactin level remains normal, it does not rule out seizure. Prolactin levels should therefore be used in combination with other testing to make a definitive diagnosis or exclusion of seizure.[8]

Anion gap and Denver Seizure Score

The anion gap has also been shown to rise after generalized seizure due to the metabolic acidosis that occurs. With a bicarbonate level of 16 mmol/L, an elevated anion gap, and normal breathing, our patient very likely had metabolic acidosis.

It is sometimes difficult to differentiate syncope from seizure, as they share several features.

The Denver Seizure Score can help differentiate these two conditions. It is based on the patient's anion gap and bicarbonate level and is calculated as follows:

$$(24 - \text{bicarbonate}) + [2 \times (\text{anion gap} - 12)]$$

A score above 20 strongly indicates seizure activity. However, this is not a definitive tool for diagnosis. Like an elevated prolactin level, the Denver Seizure Score should be used in combination with other testing to move toward a definitive diagnosis.[9]

Our patient's anion gap was 29 mmol/L and her bicarbonate level was 16 mmol/L. Her Denver Seizure Score was therefore 42, which supports this being an episode of generalized seizure activity.

Leukocytosis

The patient had a white blood cell count of 11.03×10^9/L, which was mildly elevated. She had no history of fever and no source of infection by history.

Leukocytosis is common following generalized tonic-clonic seizure. A fever may lower the seizure threshold; however, our patient was not febrile and clinically had no factors that raised concern for an underlying infection.

ANION GAP ACIDOSIS AND SEIZURE

3 Which of the following can cause both anion gap acidosis and seizure?

- ☐ Ethylene glycol
- ☐ Salicylate overdose
- ☐ Ethanol withdrawal without ketosis
- ☐ Alcoholic ketoacidosis
- ☐ Methanol

All of the above except for ethanol withdrawal without ketosis can cause both anion gap acidosis and seizure.

Many patients are not forthcoming about alcohol or drug use when talking with a physician

Ethylene glycol can cause seizure and an elevated anion gap acidosis. However, this patient had no history of ingesting antifreeze (the most common source of ethylene glycol in the home) and no evidence of calcium oxalate crystals in the urine, which would be a sign of ethylene glycol toxicity. Additional testing for ethylene glycol may include serum ethylene glycol levels and ultraviolet light testing of the urine to detect fluorescein, which is commonly added to automotive antifreeze to help mechanics find fluid leaks in engines.

Salicylate overdose can cause seizure and an elevated anion gap acidosis. However, this patient has no history of aspirin ingestion, and a serum aspirin level was later ordered and found to be negative. In addition, the acid-base disorder in salicylate overdose may be respiratory alkalosis from direct stimulation of respiratory centers in conjunction with metabolic acidosis.

Ethanol withdrawal can cause seizure and may result in ketoacidosis, which would appear as anion gap acidosis. The undetectable

ethanol level in this patient would be consistent with withdrawal from ethanol, which may also lead to ketoacidosis.

Alcoholic ketoacidosis is a late finding in patients who have been drinking ethanol and is thus a possible cause of an elevated anion gap in this patient. However, the absence of ketones in her urine speaks against this diagnosis.

Methanol can cause seizure and acidosis, but laboratory testing would reveal a normal anion gap and an elevated osmolar gap. This was not likely in this patient.

The presence of anion gap acidosis is important in forming a differential diagnosis. Several causes of anion gap acidosis may also cause seizure. These include salicylates, ethanol withdrawal with ketosis, methanol, and isoniazid. None of these appears to be a factor in this patient's case.

DIFFERENTIAL DIAGNOSIS IN OUR PATIENT

4 What is the most likely cause of this patient's seizure?

- ☐ Bupropion side effect
- ☐ Benzodiazepine withdrawal
- ☐ Ethanol withdrawal
- ☐ Brain lesion
- ☐ Central nervous system infection
- ☐ Unprovoked seizure (new-onset epilepsy)

EEG must always be interpreted in the context of the patient's history and symptoms

Bupropion, an inhibitor of neuronal reuptake of norepinephrine and dopamine, has been used in the United States since 1989 to treat major depression.[10] At therapeutic doses, it lowers the seizure threshold; in cases of acute overdose, seizures typically occur within hours of the dose, or up to 24 hours in patients taking extended-release formulations.[11]

Bupropion should be used with caution or avoided in patients taking other medications that also lower the seizure threshold, or during withdrawal from alcohol, benzodiazepines, or barbiturates.[10]

Benzodiazepine withdrawal. Abrupt cessation of benzodiazepines also lowers the seizure threshold, and seizures are commonly seen in benzodiazepine withdrawal syndrome. The use of benzodiazepines is controversial in many situations, and discontinuing them may prove problematic for both the patient and physician, as the potential for abuse and addiction is significant.

Seizures have occurred during withdrawal from even short-term benzodiazepine use. Other factors, such as concomitant use of other medications that lower the seizure threshold, may play a more significant role in causing withdrawal seizures than the duration of benzodiazepine therapy.[12]

Medications shown to be useful in managing withdrawal from benzodiazepines include carbamazepine, imipramine, valproate, and trazodone. Paroxetine has also been shown to be helpful in patients with major depression who are being taken off a benzodiazepine.[13]

Ethanol withdrawal is common in patients presenting to emergency departments, and seizures are frequently seen in these patients. This patient reported social drinking but not drinking ethanol daily, although many patients are not forthcoming about alcohol or drug use when talking with a physician or other healthcare provider.

Alcohol withdrawal seizures may accompany delirium tremens or major withdrawal syndrome, but they are seen more often in the absence of major withdrawal or delirium tremens. Seizures are typically single or occur in a short grouping over a brief period of time and mostly occur in chronic alcoholism. The role of anticonvulsants in patients with alcohol withdrawal seizure has not been established.[14]

Brain lesion. A previously undiagnosed brain tumor is not a common cause of new-onset seizure, although it is not unusual for a brain tumor to cause new-onset seizure. In 1 study, 6% of patients with new-onset seizure had a clinically significant lesion on brain imaging.[15] In addition, 15% to 30% of patients with a previously undiagnosed brain tumor present with seizure as the first symptom.[16] Patients with abnormal findings on neurologic examination after the seizure activity are more likely to have a structural lesion that may be identified by computed tomography (CT) or magnetic resonance imaging. (MRI)[15]

Unprovoked seizure occurs without an identifiable precipitating factor, or from a central nervous system insult that occurred more than 7 days earlier. Patients who may have

recurrent unprovoked seizure will likely be diagnosed with epilepsy.[15] Patients with a first-time unprovoked seizure have a 30% or higher likelihood of having another unprovoked seizure within 5 years.[17]

It is most likely that bupropion is the key factor in lowering the seizure threshold in this patient. However, patients sometimes underreport the amount of alcohol they consume, and though less likely, our patient's report of not drinking for 2 weeks may also be unreliable. Ethanol withdrawal, though unlikely, may also be a consideration with this case.

FURTHER TESTING FOR OUR PATIENT

5 Which tests may be helpful in this patient's workup?

- ☐ CT of the brain
- ☐ Lumbar puncture for spinal fluid analysis
- ☐ MRI of the brain
- ☐ Electroencephalography (EEG)

This patient had had a headache for 1 week before presenting to the emergency department. Indications for neuroimaging in a patient with headache include sudden onset of severe headache, neurologic deficits, human immunodeficiency virus infection, loss of consciousness, immunosuppression, pregnancy, malignancy, and age over 50 with a new type of headache.[18,19] Therefore, she should undergo some form of neuroimaging, either CT or MRI.

CT is the most readily available and fastest imaging study for the central nervous system available to emergency physicians. CT is limited, however, due to its decreased sensitivity in detecting some brain lesions. Therefore, many patients with first-time seizure may eventually require MRI.[15] Furthermore, patients with focal onset of the seizure activity are more likely to have a structural lesion precipitating the seizure. MRI may have a higher yield than CT in these cases.[15,20]

Lumbar puncture for spinal fluid analysis is helpful in evaluating a patient with a suspected central nervous system infection such as meningitis or encephalitis, or subarachnoid hemorrhage.

This patient had a normal neurologic examination, no fever, and no meningeal signs, and central nervous system infection was very unlikely. Also, because she had had a headache for 1 week before the presentation with seizurelike activity, subarachnoid hemorrhage was very unlikely, and emergency lumbar puncture was not indicated.

MRI is less readily available than CT in a timely fashion in most emergency departments in the United States. It offers a higher yield than CT in diagnosing pathology such as acute stroke, brain tumor, and plaques seen in multiple sclerosis. CT is superior to MRI in diagnosing bony abnormalities and is very sensitive for detecting acute bleeding.

If MRI is performed, it should follow a specific protocol that includes high-resolution images for epilepsy evaluation rather than the more commonly ordered stroke protocol. The stroke protocol is more likely to be ordered in the emergency department.

EEG is well established in evaluating new-onset seizure in pediatric patients. Studies also demonstrate its utility in evaluating first-time seizure in adults, providing evidence that both epileptiform and nonepileptiform abnormalities seen on EEG are associated with a higher risk of recurrent seizure activity than in patients with normal findings on EEG.[1]

EEG may be difficult to interpret in adults. According to Benbadis,[5] as many as one-third of adult patients diagnosed with epilepsy on EEG did not have epilepsy. This is because of normal variants, simple fluctuations of background rhythms, or fragmented alpha activity that can have a similar appearance to epileptiform patterns. EEG must always be interpreted in the context of the patient's history and symptoms.[5]

Though EEG has limitations, it remains a crucial tool for identifying epilepsy. Following a single seizure, the decision to prescribe antiepileptic drugs is highly influenced by patterns on EEG associated with a risk of recurrence. In fact, a patient experiencing a single, idiopathic seizure and exhibiting an EEG pattern of spike wave discharges is likely to have recurrent seizure activity.[21] Also, the appropriate use of EEG after even a single unprovoked seizure can identify patients with epilepsy and a risk of recurrent seizure greater than 60%.[21,22]

Every year, about 180,000 US adults have a first seizure, and 10% of Americans experience at least 1 seizure during their lifetime

NO FURTHER SEIZURES

The patient was admitted to the observation unit from the emergency department after undergoing CT without intravenous contrast. While in observation, she had no additional episodes, and her vital signs remained within normal limits.

She underwent MRI and EEG as well as repeat laboratory studies and consultation by a neurologist. CT showed no structural abnormality, MRI results were read as normal, and EEG showed no epileptiform spikes or abnormal slow waves or other abnormality consistent with seizure. The repeat laboratory studies revealed normalization of the prolactin level at 11.3 ng/mL (reference range 2.0–17.4).

The final impression of the neurology consultant was that the patient had had a seizure that was most likely due to recently starting bupropion in combination with the withdrawal of the benzodiazepine, which lowered the seizure threshold. The neurologist also believed that our patient had no findings or symptoms other than the seizure that would suggest benzodiazepine withdrawal syndrome. According to the patient's social history, it was unlikely that she had the pattern of alcohol consumption that would result in ethanol withdrawal seizure.

Seizures are common. In fact, every year, 180,000 US adults have their first seizure, and 10% of Americans will experience at least 1 seizure during their lifetime. However, only 20% to 25% of seizures are generalized tonic-clonic seizures as in our patient.[23]

As this patient had an identifiable cause for the seizure, there was no need to initiate anticonvulsant therapy at the time of discharge. She was discharged to home without any anticonvulsant, the bupropion was discontinued, and the lorazepam was not restarted. When contacted by telephone at 1 month and 18 months after discharge, she reported she had not experienced any additional seizures and has not needed antiepileptic medications.

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