Clinical Reasoning:

A 62-year-old woman with bizarre behavior and recurrent episodes of behavioral arrest

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SECTION 1

A 62-year-old woman was brought to the emergency department by family members after experiencing 3 episodes of behavioral and speech arrest over the past day, with the third episode reportedly ending in convulsive shaking. Her medical history was significant for chronic abdominal and low back pain, for which she had been taking diazepam for the past 9 years, at a stable dose of 10 mg 4 times daily, in addition to tramadol 50–100 mg every 6 hours as needed. She also had a history of migraine headaches and was taking Topamax 100 mg twice daily. There was no history of seizure.

She had 2 events while in the emergency department, one of which was witnessed by the neurology team and consisted of sudden behavioral arrest and decreased responsiveness. She attended to the examiner when her name was called; however, she did not verbally respond or follow commands. The event lasted 5 minutes and ended when she suddenly interrupted a side conversation regarding MRI, to state

that she was allergic to contrast dye. She was then immediately oriented and able to answer questions. In between these spells, the patient exhibited pressured, tangential speech with some verbal perseveration and ideas of grandeur. Her behavior was described in nursing notes as “disinhibited and silly,” but she was otherwise alert and oriented. Her neurologic examination was otherwise unremarkable, with the exception of brisk but symmetric reflexes. CT head was without acute abnormality and blood count and chemistry including electrolytes, liver function tests, thyroid-stimulating hormone, urinalysis, and urine drug screen were unremarkable.

The patient continued to have similar spells overnight as described above.

Questions for consideration:

1. What is on your differential at this time?
2. What other things do you want to know?
3. What testing would you like to perform?

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SECTION 2

The differential diagnosis at this time was broad. The differential diagnoses of discrete stereotyped events in this case included epileptic seizures, nonepileptic spells, benzodiazepine withdrawal seizures, and migraines. However, as the patient's baseline mental status was unclear to the team at presentation, further diagnoses of altered mental status were considered as well, including nonconvulsive status epilepticus (NCSE), psychiatric disturbance, and toxic/metabolic encephalopathy. On further questioning, the patient admitted to abrupt cessation of her valium 3–4 days prior to admission as she ran out of her prescription. Given this information, there was high suspicion for benzodiazepine discrete withdrawal seizures or benzodiazepine-associated NCSE. Therefore, the patient was put on continuous video EEG monitoring, which captured several

spells. These were similar to those described previously. During one such episode, the patient picked up her cell phone, pressing the touchscreen several times, then held the phone up to her head. She said, "Hello, huh? I'm fine. No, I'm fine, um—I'm great," followed by apparent behavioral arrest lasting several minutes. Following this, she began waving her arms around, smiling, then laughing. She said to the staff at bedside, "I can function," while gesturing with her hands. She said, "I am still seeing... it is pleasant. Everything is going on." She answered all orientation questions correctly.

Excerpts of the EEG are depicted in the figure.

Questions for consideration:

1. What is your diagnosis?
2. What is the next step in management?

GO TO SECTION 3

Figure EEG shows the frequency of stereotyped episodes and corresponding ictal activity over approximately 20 hours

The amplitude integrated EEG measured on channel C3-C4 is shown with amplitude (y-axis) shown over time (x-axis), showing the frequency of stereotyped episodes and corresponding ictal activity over approximately 20 hours. Samples of EEG are also shown during (A) period of low-amplitude mixed frequencies and (B) period of continuous, generalized, rhythmic to quasi-rhythmic irregular spike-and-slow wave discharges.

SECTION 3

Continuous EEG revealed background activities of relatively low amplitude, mixed frequency activities interrupted by long runs of continuous, generalized, rhythmic to quasi-rhythmic, irregular 2–3 Hz spike-and-slow wave activities occurring every 20–40 minutes, with these periods of spike-and-slow wave activity correlating with stereotyped episodes. Based on EEG findings, the patient was treated acutely with 1 mg IV ativan, loaded with 20 mg/kg IV Depakote, and her home valium was resumed. Her episodes resolved and her EEG improved, demonstrating resolution of the spike-and-slow wave activity and return of normal waking background activity. Her labile affect and concentration improved. Clinical and electrographic improvement following administration of benzodiazepine and antiepileptic drug (AED) treatment suggests the diagnosis of NCSE. Her MRI brain revealed only small 4 mm left periorbital aneurysm, unchanged from prior studies and of doubtful significance. She was discharged on maintenance valproate 750 mg BID, and her tramadol was discontinued. She was seen in follow-up 8 weeks later, and was noted to have normal mental status and language function at that time. A follow-up routine EEG revealed enhanced beta activity but no evidence of epileptiform discharges.

DISCUSSION We describe a case of NCSE due to abrupt benzodiazepine withdrawal in a 62-year-old woman with no prior seizure history or predisposing factors. Isolated seizures in the setting of benzodiazepine withdrawal are well-described; however, reports of NCSE in this setting are rare. The association of benzodiazepine withdrawal seizure was first recognized in the 1980s in reports of acute confusional states with EEG changes associated with sedative-hypnotic abuse and withdrawal.¹ Few cases have been reported since then, although recently, 2 cases were described in the literature of focal, self-limited, nonconvulsive seizures that occurred during benzodiazepine detoxification with flumazenil, which were described as acute episodes of decreased responsiveness and minimal response to commands.²

The first cases of NCSE related to benzodiazepine withdrawal were reported in the early 1990s in a case series of 11 adults with NCSE defined as a heterogeneous syndrome with fluctuating mental status changes associated with varied motor manifestations and EEG with variable findings, including 3-Hz spike wave. A precipitating factor of benzodiazepine withdrawal was implicated in 8 of these patients. Clinical presentations included moderate confusion, disorientation, retained ability to follow

simple commands but difficulty with complex commands, and reduced language output. Automatisms, facial myoclonus, bilateral Babinski, and ataxic gait were also reported.³ A female predominance has also been noted.^{3,4}

The diagnosis of NCSE is often challenging, as there has historically been a lack of evidence-based diagnostic criteria or consensus on electrographic patterns of status epilepticus. We based our diagnosis on recommendations from a proposed unified terminology and classification system presented by Beniczky et al.⁵ suggesting specific EEG findings associated with clinical changes to make a diagnosis. In our patient, specifically, the EEG pattern of rhythmic epileptiform discharges of 2–3 Hz associated with EEG and clinical improvement following IV AED administration would meet these criteria of a diagnosis of NCSE.

All benzodiazepines act by binding to the GABA_A receptor, potentiating inhibitory GABAergic action. Long-term exposure to benzodiazepines leads to adaptation, with downregulation of GABAergic inhibition as well as upregulation of the glutamatergic system. Abrupt withdrawal of benzodiazepine unmasks this change and results in diffuse rebound cortical excitability, which is the suspected mechanism behind benzodiazepine withdrawal seizure activity.⁴ Treatment includes reinstitution of benzodiazepine, and most patients are initially placed on antiepileptic therapy, but the vast majority have no return of symptoms and do not require long-term AED treatment.^{3,6–8} Indeed, the largest barrier to treating this entity is recognizing it. Despite the mentioned case reports, there continues to be diagnostic delay in these patients,^{6–8} presumably because NCSE remains low on the differential, and is only investigated once other etiologies are ruled out. This case illustrates an important, treatable etiology for confusional state in the setting of acute benzodiazepine withdrawal, and emphasizes the need for early suspicion and the importance of emergent EEG in such cases.

AUTHOR CONTRIBUTIONS

Halley Briglia: research, report drafting and editing. Scott Kohler: EEG interpretation, creation of figures. Jennifer Langer: report editing and overview, clinical expertise.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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Neurology 2016;86:e62-e65

DOI 10.1212/WNL.0000000000002367

This information is current as of February 15, 2016

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