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A 41-year-old woman with confusion and unsteady gait

A 41-YEAR-OLD WOMAN presents to the emergency department because of confusion and an unstable gait. The symptoms began gradually 3 days previously and persisted, and on the present day she developed headache, slurred speech, neck stiffness, and nausea without vomiting. She says she has no photophobia, fever, chills, chest pain, dyspnea, abdominal pain, rash, or change in her stools. She did not have these symptoms in the past and has not traveled outside the state of Ohio for the previous 6 months.

Medical history. The patient has a history of epilepsy diagnosed 7 years ago, and has not had a seizure for 7 years while compliant with her medications. A recent computed tomographic (CT) scan of her head was normal. She also has a history of hypertension, peptic ulcer disease, trigeminal neuralgia, temporomandibular joint syndrome, depression, and schizophrenia. She has smoked one pack per day for the past 20 years and denies using alcohol or illicit drugs.

The patient's medications include sertraline, risperidone, lorazepam, hydrocodone with acetaminophen, carbamazepine, verapamil, hydralazine, cyclobenzaprine, ranitidine, estrogen, and medroxyprogesterone. She is compliant with all of her medications, and she sees her physician regularly.

PHYSICAL EXAMINATION

The patient's temperature is 98.4°F (36.9°C), pulse rate 112, respiratory rate 18, blood pressure 124/77 mm Hg, and O_2 saturation 99% by pulse oximetry while breathing room air.

The patient appears generally healthy, though she is drowsy and has slurred speech. She is oriented to person, place, and time. Her muscle strength is 5 on a scale of 5 in all major muscle groups. Sensation is intact bilaterally; however, she has an unsteady gait, dysmetria, and dysdiadochokinesia (FIGURE 1). Her pupils are equal, midrange, and slow to react to light bilaterally. Her fundi are grossly normal bilaterally. The extraocular muscle movements are normal, evoked lateral-gaze nystagmus is present bilaterally, and cranial nerves II through XII are intact. Her neck is supple and nontender without a goiter, mass, or carotid bruits. Brudzinski sign and Kernig sign are absent (FIGURE 1).

Her lungs are clear to auscultation. Her heart has a regular rhythm and no murmur. Her abdomen is soft and nontender with normal bowel sounds and no hepatosplenomegaly. The rectal exam reveals no mass, normal sphincter tone, and heme-negative stool.

Initial laboratory studies show a white blood cell count of 10.6 × 10^9/L (normal: 4–11) with 90% neutrophils (normal: 40%–70%). The hemoglobin level is 9.7 g/dL (normal: 12.0–16.0), and the hematocrit is 30.1% (normal: 37%–47%). Serum levels of sodium, potassium, chloride, CO_2, blood urea nitrogen, creatinine, and glucose are all within normal limits.

The patient regularly takes 12 different medications

DIFFERENTIAL DIAGNOSIS

1 What is the most likely cause of this patient's symptoms?

- ❑ Cerebellar tumor
- ❑ Cerebellar infarction
- ❑ Subdural hematoma
- ❑ Opiate intoxication
- ❑ Carbamazepine intoxication
- ❑ Central nervous system infection

TABLE 1

Drugs that decrease carbamazepine metabolism

Danazol
Diltiazem
Fluoxetine
Histamine receptor antagonists (eg, cimetidine, loratadine, terfenadine)
Isoniazid
Itraconazole
Ketoconazole
Macrolide antibiotics (eg, erythromycin, clarithromycin, troleandromycin)
Nicotinamide
Propoxyphene
Valproic acid
Verapamil

All of the above are possibilities that should be considered.

Cerebellar tumors, such as gliomas or metastatic lesions to the cerebellum, frequently produce a subacute unilateral or focal ataxia. A cerebellar lesion may also be responsible for slurred speech similar to that in alcohol intoxication.

The first sign of carbamazepine toxicity is evoked lateral-gaze nystagmus

Cerebellar infarction due to posterior circulation compromise may result in life-threatening respiratory arrest due to edema and increased intracranial pressure. Common early signs include gait disturbance, nausea, and vomiting, followed by slurred speech, cephalgia, neck pain, and lethargy. A "drop attack" in which the patient complains of a sudden inability to walk or stand may be the presenting complaint. Physical findings include ataxia, bilateral facial weakness, and dysarthria.[1]

Subdural hematoma may be acute or chronic. Acute subdural hematomas are occasionally diagnosed immediately after severe trauma, but typically present 2 to 14 days later.

In contrast, by definition chronic subdural hematomas occur more than 2 weeks after the injury. In up to 30% of cases there is no clear trauma or history of trauma; this is far more prevalent in patients with significant cerebral atrophy such as alcohol abusers and the elderly, who also have a higher mortality rate. The signs and symptoms of chronic subdural hematoma include altered level of consciousness, weakness, nausea, vomiting, headache, and neck pain.

Opiate intoxication is a common cause of unsteady gait and altered mental status. Knowing a patient's history of opiate use, including dosage, is most helpful, as the physical findings are nonspecific: eg, altered mental status, respiratory depression, meiosis, and noncardiogenic pulmonary edema. The specific opiate responsible is significant because different opiates have different durations of action, though the treatment is largely the same.

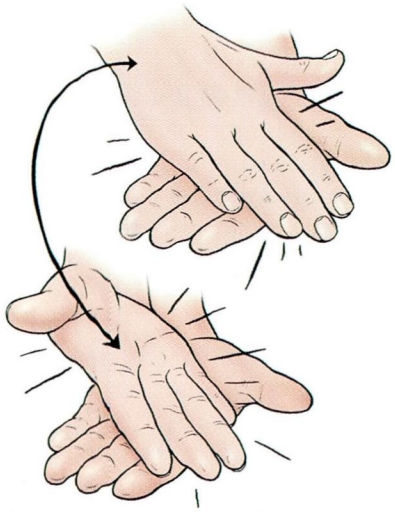
Carbamazepine intoxication is becoming more common as more patients take this drug for seizure disorders, chronic pain, and mood disorders. The side effects of carbamazepine (Tegretol, Carbatrol) include convulsions, depressed mental status, coma, ataxia, diplopia, cephalgia, slurred speech, dizziness, bradycardia, tachycardia, hyponatremia, hypocalcemia, agitation, and activation of latent psychosis.[2–4] In addition, because carbamazepine is structurally similar to imipramine and desipramine, it may cause anticholinergic symptoms in an overdose.

In most patients, the first sign of toxicity is evoked lateral-gaze nystagmus.[5] Acute neurologic symptoms typically occur at serum levels greater than 10 μg/mL.[6] Concomitant use of some antibiotics, histamine receptor antagonists, calcium channel antagonists, serotonin reuptake inhibitors, and anticonvulsants may result in elevated carbamazepine levels (TABLE 1).[7]

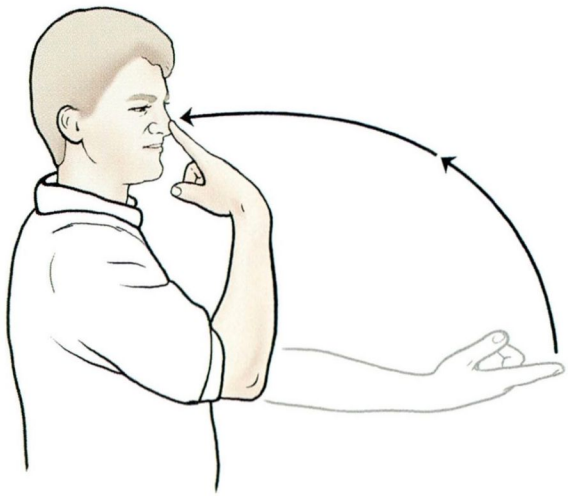
Central nervous system infections. Viral encephalitis accounts for approximately 20,000 cases in the United States each year.[8] Signs and symptoms of viral encephalitis include fever, malaise, headache, nausea, lethargy, neck stiffness, general weakness, and ataxia. Viral encephalitis is extremely difficult to diagnose on the basis of clinical findings alone, and cerebral spinal fluid and serologic studies are needed to confirm the diagnosis.

Aseptic meningitis may resemble bacterial meningitis in its presentation. Cerebral spinal fluid studies and opening pressures

Tests for cerebellar disease

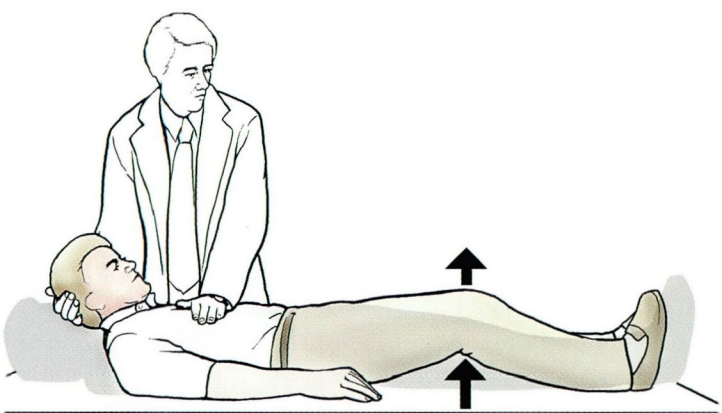


Dysdiadochokinesia is the inability to perform rapidly alternating movements. Ask the patient to hold one hand still and rapidly pat it with the palm and with the back of the other hand. Look for gross overshooting, undershooting, or confusion.

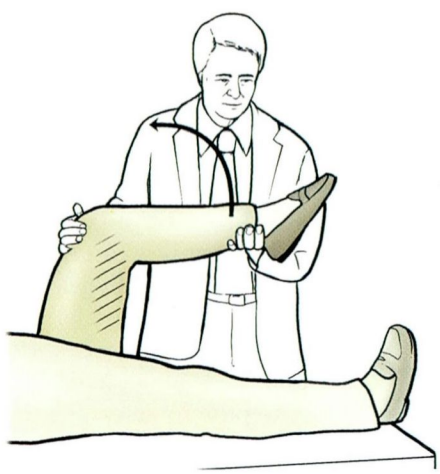


Dysmetria is the inability to estimate distances in movements, or the inability to control the amount of force needed to effect movements. Have the patient keep his or her eyes open, extend his elbow, and bring his index finger up in a wide arc to touch the tip of his nose. Look for any tremor. Repeat with the eyes closed and look for inaccuracy in aim.

Tests for meningeal irritation



Brudzinski sign. With the patient supine, hold the thorax down on the bed and passively raise the patient's head. Look for involuntary flexion of the hips and knees.



Kernig sign. With the patient supine, flex the hip and knee to 90°. Then attempt to extend the knee. Look for resistance, and pain in the hamstring muscles.

FIGURE 1

should be checked. The fluid shows a lymphocytic pleocytosis, mildly elevated protein, and normal glucose levels but no bacteria.[8]

EVALUATION

2 What additional tests are indicated?

- ❑ Serum ethanol level
- ❑ Serum carbamazepine level
- ❑ CT scan of the head
- ❑ Urine toxicology screen
- ❑ Cerebrospinal fluid analysis

All of the above would be appropriate, and our patient underwent most of them. The results of her workup are as follows:

Serum ethanol level—undetectable

Serum carbamazepine level—22.8 µg/mL (therapeutic range: 8.0–12.0 µg/mL)

CT scan of the head (without contrast)—negative for bleeding, significant atrophy, mass, mass effect, or infarction

Urine toxicology screen—negative for opiates, cocaine, and phencyclidine

Serum tricyclic antidepressant level—225 ng/mL (normal: < 20 ng/mL). (However, the patient denied ever taking any antidepressant other than sertraline. An explanation may be that carbamazepine is structurally similar to some of the tricyclic antidepressants, and carbamazepine levels greater than 20 µg/mL can cross-react with the assay and cause falsely elevated levels. In addition, cyclobenzaprine [Flexeril] levels of greater than 0.3 µg/mL may do the same when the AxSYM Tricyclic Antidepressant assay is used, as in this case.[9])

Carbamazepine at toxic levels can cause falsely elevated tricyclic antidepressant levels

Electrocardiogram—sinus tachycardia without any other abnormalities

Cerebrospinal fluid studies—not obtained, in view of the diagnosis of carbamazepine toxicity.

THERAPY

3 What should be the first step in treating this patient?

- ❑ Induce emesis
- ❑ Gastric lavage
- ❑ Orally administered activated charcoal
- ❑ Whole-bowel irrigation
- ❑ Sodium bicarbonate
- ❑ Hemodialysis
- ❑ Charcoal hemoperfusion

The patient received 60 grams of activated charcoal by mouth and was admitted to the clinical decision unit for 23 hours of observation, supportive care, and repeat doses of activated charcoal if needed.

Activated charcoal is thought to reduce carbamazepine toxicity by two mechanisms: direct binding of the drug in the intestinal lumen, and binding of the drug and its metabolites presented a second time to the gut by enterohepatic circulation.

There are several rationales for giving multiple doses of activated charcoal. Carbamazepine follows first-order kinetics with a half-life of 16 to 26 hours. Multiple doses of activated charcoal reduce the half-life of carbamazepine to 8.6 hours.[9,10] In addition, gastric emptying may be delayed in carbamazepine toxicity, owing to the drug's anticholinergic effects. For this reason, delayed absorption is common in cases of acute overdose,[9] but can be prevented by giving multiple doses of activated charcoal.

Some authors advocate obtaining the level of free carbamazepine rather than total carbamazepine levels, since it is generally believed that only free drug is responsible for the clinical effects. However, others point out that the clinical picture over time is more useful in managing the patient's condition than either free or total drug levels.[10] In fact, some advocate giving multiple doses of activated charcoal to all patients in whom symptoms do not rapidly resolve.[11]

As this patient has chronic carbamazepine toxicity, there is no role for induced emesis, gastric lavage, or whole-bowel irrigation. Also, these procedures could produce a rapid drop in the serum carbamazepine level, which could precipitate seizures in a patient with an underlying seizure disorder, such as this patient.

Alkalization of the urine is useful for treating a tricyclic antidepressant overdose, but giving sodium bicarbonate to treat cardiac conduction abnormalities or dysrhythmias due to carbamazepine toxicity has not been shown to be beneficial.[3]

Charcoal hemoperfusion is useful in treating severe carbamazepine overdose, but is indicated only if the patient is likely to become unstable.

There is no role for hemodialysis in treating carbamazepine toxicity, because the drug is not very water-soluble.

CARDIAC ADVERSE EFFECTS OF CARBAMAZEPINE

4 Which cardiac effects are *not* associated with carbamazepine toxicity?

- ❑ Sinus tachycardia
- ❑ Sinus bradycardia
- ❑ Complete heart block
- ❑ QT segment prolongation
- ❑ Atrial fibrillation
- ❑ Depression of the idioventricular rhythm

The most common cardiac finding in carbamazepine toxicity is sinus tachycardia, which is attributed to the drug's anticholinergic properties. On the other hand, because carbamazepine has negative chronotropic and dromotropic effects, bradycardia may be seen.

Other dysrhythmias and conduction abnormalities, including complete heart block, QTc prolongation, and depression of the idioventricular rhythm, have also been described in patients with cardiomyopathy and in the elderly. For this reason, some physicians advocate 24-hour cardiac monitoring of elderly patients and those with cardiomyopathy, after neurologic symptoms resolve and carbamazepine levels decrease.[12–14] Atrial fibrillation is not associated with carbamazepine toxicity.

OTHER ADVERSE EFFECTS OF CARBAMAZEPINE

Up to 30% of patients taking carbamazepine experience one or more side effects. The most common adverse effects encountered with therapeutic or toxic levels of carbamazepine are neurologic, as previously mentioned. However, the following adverse reactions are not related to toxic levels.

Hematologic effects. Aplastic anemia occurs at a rate of 0.5 cases per 100,000 patients per year. This condition has no specific treatment and may be fatal. Persistent leukopenia occurs in 10% of patients, and agranulocytosis, thrombocytopenia, and pancytopenia may occur.[13]

Gastrointestinal symptoms associated with carbamazepine include anorexia, nausea, vomiting, and diarrhea.

Metabolic effects include depressed thyroid function and water retention with hyponatremia similar to the syndrome of inappropriate secretion of antidiuretic hormone.[6] Elevations in serum bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) may be seen and are relatively benign. Acute hepatic failure is an extremely rare complication of carbamazepine use and may be fatal.

Skin manifestations include photosensitivity, erythema, exfoliative dermatitis, and Stevens-Johnson syndrome.

HOSPITAL COURSE

The patient stayed overnight in the clinical decision unit, where she received intravenous normal saline and all of her regularly prescribed medications as directed before her admission, except for carbamazepine. After an uneventful observation period, her repeat carbamazepine level was 12.5 µg/mL on the following morning. Her confusion, ataxia, and tachycardia resolved, and her mental status returned to normal. She did not require another dose of activated charcoal, and she was discharged to home in good condition 5 hours after the repeat level was obtained, with instructions to decrease her daily carbamazepine dosage. The etiology of her anemia was unclear at the time of discharge, with workup to be completed on an outpatient basis.

Carbamazepine's half-life is 16 to 26 hours

REFERENCES

1. **Ropper AH.** Traumatic injuries of the head and spine. In Fauci AS, Braunwald E, Isselbacher KJ, et al, editors. Harrison's Principles of Internal Medicine. 14th ed. New York; McGraw-Hill, 1998:2439–2451.
2. **Berger H.** An unusual manifestation of Tegretol (carbamazepine) toxicity. Ann Intern Med 1971; 74:449–450.
3. **Hessler R.** Cardiovascular principles. In Goldfrank LR, editor. Goldfrank's Toxicologic Emergencies, 6th ed. Stamford, CT; Appleton & Lang, 1998:353–373.
4. **Wax PM.** Antidotes in depth. In Goldfrank LR, editor. Goldfrank's Toxicologic Emergencies, 6th ed. Stamford, CT; Appleton & Lang, 1998:582–589.
5. **Specht U, May T, Rohde M.** Cerebellar atrophy decreases the threshold of carbamazepine toxicity in patients with chronic focal epilepsy, Arch Neurol 1997; 54:427–431.

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6. **Albani F, Riva R, Baruzzi A.** Carbamazepine clinical pharmacology: A review. Pharmacopsychiatry 1995; 28:235–224.
7. **Doyon S.** Anticonvulsants. In Goldfrank LR, editor. Goldfrank's Toxicologic Emergencies. 6th ed. Stamford, CT; Appleton & Lang, 1998:489–499.
8. **Tyler KL.** Aseptic meningitis, viral encephalitis, and prion disease. In Fauci AS, Braunwald E, Isselbacher KJ, et al, editors. Harrison's Principles of Internal Medicine. 14th ed. New York; McGraw-Hill, 1998:2439–2451.
9. **Boldy D, Heath A, Ruddock S, et al.** Activated charcoal for carbamazepine poisoning [letter]. Lancet 1987; 1:1027.
10. **Sullivan JB, Barry MD, Rumack MD, Peterson RG.** Acute carbamazepine toxicity resulting from overdose. Neurology 1981; 31:621–624.
11. **Sethna M, Solomon G, Cedarbaum J, Kutt H.** Successful treatment of massive carbamazepine overdose. Epliepsia 1989; 30:71–73.
12. **Apfelbaum JD, Caravati Em, Kerns WP 2nd, et al.** Cardiovascular effects of carbamazepine toxicity. Ann Emerg Med 1995; 25:631–635.
13. **Lawless L.** Acute carbamazepine toxicity resulting from overdose [letter]. Neurology 1982; 32:328–329.
14. **Durelli L, Massazza U, Cavallo R.** Carbamazepine toxicity and poisoning: Incidence, clinical features and management. Med Toxicol Adverse Drug Exp 1989; 4:95–110.

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LETTER TO THE EDITOR

Gulf War syndrome

(JANUARY 2000)

TO THE EDITOR: It was quite interesting to note the various causes of Gulf War syndrome proposed by Dr. Frost.[1] Numerous reports have shown that the Gulf War itself has not made people sick.[2] I think if people anywhere are exposed to any kind of human slaughter or war, they are bound to get symptoms quite unusual to others. Chronic fatigue syndrome is the most common symptom I have come across. Dysfunction of the nervous system and post-traumatic stress disorder have been quite infrequent.

Physicians must carefully evaluate patients who are veterans of the Persian Gulf War to further our knowledge and confirm the existence of this syndrome. Thanks for the article.

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REFERENCES

1. **Frost SD.** Gulf War syndrome: Proposed causes. Cleve Clin J Med 2000; 67:17–20.
2. **Gray GC, Smith TC, Kang HK, Knoke JD.** Are Gulf War veterans suffering war-related illnesses? Federal and civilian hospitalizations examined, June 1991 to December 1994. Am J Epidemiol 2000; 151:63–71.