Young, angry, and in need of a liver transplant

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Ms. L, age 21, takes sertraline for depression. Two weeks after being prescribed valproic acid for 'mood swings,' she comes to the ED with acute liver failure. Is her liver injury drug-induced?

CASE Rash, fever, extreme lethargy; multiple hospital visits

Ms. L, age 21, a single woman with a history of major depressive disorder (MDD), is directly admitted from an outside community hospital to our tertiary care academic hospital with acute liver failure.

One month earlier, Ms. L had an argument with her family and punched a wall, fracturing her hand. Following the episode, Ms. L's primary care physician (PCP) prescribed valproic acid, 500 mg/d, to address "mood swings," which included angry outbursts and irritability. According to her PCP, no baseline laboratory tests were ordered for Ms. L when she started valproic acid because she was young and otherwise healthy.

After Ms. L had been taking valproic acid for approximately 2 weeks, her mother noticed she became extremely lethargic and took her to the emergency department (ED) of a community hospital (Visit 1) (***Table 1***, ***page 47***). At this time, her laboratory results were notable for an aspartate aminotransferase (AST) level of 303 IU/L (reference range: 8 to 40 IU/L) and an alanine aminotransferase (ALT) level of 241 IU/L (reference range: 20 to 60 IU/L). She also underwent a liver ultrasound, urine toxicology screen, blood alcohol level, and acetaminophen level; the results of all of these tests were unremarkable. Her valproic acid level was within therapeutic limits, consistent with patient adherence; her ammonia level was within normal limits. At Visit 1, Ms. L's transaminitis was presumed to be secondary to valproic acid. The ED clinicians told her to stop taking valproic acid and discharged her. Her PCP did not give her any follow-up instructions for further laboratory tests or any other recommendations.

During the next week, even though she stopped taking the valproic acid as instructed, Ms. L developed a rash and fever, and continued to have lethargy and general malaise. When she returned to the ED (Visit 2) (***Table 1***, ***page 47***), she was febrile, tachycardic, and hypotensive, with an elevated white blood cell count, eosinophilia, low platelets, and elevated liver function tests. At Visit 2, she was alert and oriented to person, place, time, and situation. Ms. L insisted that she had not overdosed on any medications, or used illicit drugs or alcohol. A test for hepatitis C was negative. Her ammonia level was 58 µmol/L (reference range: 11 to 32 µmol/L). Ms. L received *N*-acetylcysteine (NAC), prednisone, diphenhydramine, famotidine, and

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How would you handle this case?

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ibuprofen before she was transferred to our tertiary care hospital.

When she arrives at our facility (Visit 3) (***Table 1***, ***page 47***), Ms. L is admitted with acute liver failure. She has an ALT level of 4,091 IU/L, and an AST level of 2,049 IU/L. Ms. L's mother says that her daughter had been taking sertraline for depression for "some time" with no adverse effects, although she is not clear on the dose or frequency. Her mother says that Ms. L generally likes to spend most of her time at home, and does not believe her daughter is a danger to herself or others. Ms. L's mother could not describe any episodes of mania or recurrent, dangerous anger episodes. Ms. L has no other medical history and has otherwise been healthy.

On hospital Day 2, Ms. L's ammonia level is 72 µmol/L, which is slightly elevated. The hepatology team confirms that Ms. L may require a liver transplantation. The primary team consults the inpatient psychiatry consultation-liaison (C-L) team for a pre-transplant psychiatric evaluation.

What could be causing Ms. L's current acute liver failure?

a) medication overdose
b) acetaminophen toxicity
c) valproic acid hepatotoxicity
d) autoimmune hepatitis

The authors' observations

The differential diagnosis for Ms. L was broad and included both accidental and intentional medication overdose. The primary team consulted the inpatient psychiatry C-L team not only for a pre-transplant evaluation, but also to assess for possible overdose.

A review of the records from Visit 1 and Visit 2 at the outside hospital found no acetaminophen in Ms. L's system and verified that there was no evidence of a current valproic acid overdose. Ms. L had stated that she had not overdosed on any other medications or used any illicit drugs or alcohol. Ms. L's complex symptoms—namely fever, acute liver failure, and rash—were more consistent with an adverse effect of valproic acid or possibly an inherent autoimmune process.

Liver damage from valproic acid

Valproic acid is FDA-approved for treating bipolar disorder, epilepsy, and migraine headaches[1] (***Table 2***,[1] ***page 48***). Common adverse effects include nausea, vomiting, sleepiness, and dry mouth. Rarely, valproic acid can impair liver function. While receiving valproic acid, 5% to 10% of patients develop elevated ALT levels, but most are asymptomatic and resolve with time, even if the patient continues taking valproic acid.[2] Valproic acid hepatotoxicity resulting in liver transplantation for a healthy patient is extremely rare (***Table 3***,[1] ***page 49***). Liver failure, both fatal and non-fatal, is more prevalent in patients concurrently taking other medications, such as antiepileptics, benzodiazepines, and antipsychotics, as compared with patients receiving only valproic acid.[3]

There are 3 clinically distinguishable forms of hepatotoxicity due to valproic acid[2]:

- hyperammonemia
- acute liver failure and jaundice
- Reye-like syndrome, which is generally seen in children.

In case reports of hyperammonemia due to valproic acid, previously healthy patients experience confusion, lethargy, and eventual coma in the context of elevated serum ammonia levels; these symptoms resolved upon discontinuing valproic acid.[4,5] Liver function remained normal, with normal to near-normal liver enzymes and bilirubin.[3] Hyperammonemia and resulting encephalopathy generally occurred within 1 to 3 weeks after initiation of valproate therapy, with resolution of hyperammonemia and resulting symptoms within a few days after stopping valproic acid.[2-4]

At Visit 2, Ms. L's presentation was not initially consistent with hepatic encepha-

Clinical Point

While receiving valproic acid, 5% to 10% of patients experience elevated ALT levels, but most are asymptomatic

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Table 1

Ms. L: Timeline of events

Week 0	Week 2	Week 3		Week 4	Week 6
Valproic acid initiation	Visit 1: ED at community hospital	Visit 2: ED at community hospital	Visit 3: Transfer from community hospital to tertiary academic hospital	Visit 3: Liver transplant	Hospital discharge
Treatment for mood instability (anger outburst and irritability)	Lethargy Elevated AST/ALT	Elevated AST/ALT Fever Elevated WBCs Elevated heart rate Low blood pressure	Rash Confusion	Elevated PT/INR	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ED: emergency department; INR: international normalized ratio; PT: prothrombin time; WBCs: white blood cells

lopathy. She was alert and oriented to person, place, time, and situation. Additionally, Ms. L's presenting problem was elevated liver function tests, not elevated ammonia levels. At Visit 2, her ammonia level was 58 µmol/L; on Day 2 (Visit 3) of her hospital stay, her ammonia level was 72 µmol/L (slightly elevated).

At Visit 2 in the ED, Ms. L was started on NAC because the team suspected she was experiencing drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. This syndrome is characterized by extensive rash, fever, and involvement of at least 1 internal organ. It is a variation of a drug-induced hypersensitivity syndrome. Ms. L's unremarkable valproic acid levels combined with the psychiatry assessment ruled out valproic hepatotoxicity due to overdose, either intentional or accidental.

In case reports, patients who developed acute liver failure due to valproic acid typically had a hepatitis-like syndrome consisting of moderate elevation in liver enzymes, jaundice, and liver failure necessitating transplantation after at least 1 month of treatment with valproic acid.[2] In addition to the typical hepatitis-like syndrome resulting from valproic acid, case reports have also linked treatment with valproic acid to DRESS syndrome.[2] This syndrome is known to occur with anticonvulsants such as phenobarbital, lamotrigine, and phenytoin, but there are only a few reported cases of DRESS syndrome due to valproic acid therapy alone.[6] Drug rash with eosinophilia and systemic symptoms syndrome differs from other acute liver failure cases in that patients also develop lymphadenopathy, fever, and rash.[2,6,7] Patients with DRESS syndrome typically respond to corticosteroid therapy and discontinuation of valproic acid, and the liver damage resolves after several weeks, without a need for transplantation.[2,6,7]

Ms. L seemed to have similarities to DRESS syndrome. However, the severity of her liver damage, which might require transplantation even after only 2 weeks of valproic acid therapy, initially led the hepatology and C-L teams to consider her presentation similar to severe hepatitis-like cases.

EVALUATION Consent for transplantation

As an inpatient, Ms. L undergoes further laboratory testing. Her hepatic function panel demonstrates a total protein level of 4.8 g/dL, an albumin level of 2.0 g/dL, total

Clinical Point

Ms. L had symptoms similar to DRESS syndrome, but there are few cases of this syndrome being the result of valproic acid therapy alone

Table 2

Valproic acid indications and contraindications

FDA-approved indications	Contraindications
Epilepsy	Hepatic disease or severe hepatic dysfunction
Migraine prophylaxis (not in women of childbearing age)	Known hypersensitivity to this medication
Treatment of mania from bipolar disorder	Urea cycle disorders

Source: Adapted from reference 1

Clinical Point

Supplementation with L-carnitine may increase survival from severe hepatotoxicity due to valproic acid

bilirubin level of 12.2 mg/dL, and alkaline phosphatase of 166 IU/L. Her laboratory results indicate a prothrombin time (PT) of 77.4 seconds, partial thromboplastin time of 61.5 seconds, and PT international normalized ratio (INR) of 9.6. Ms. L's basic metabolic panel is within normal limits except for a blood urea nitrogen level of 6 mg/dL, glucose level of 136 mg/dL, and calcium level of 7.0 mg/dL. Her complete blood count indicates a white blood cell count of 12.1, hemoglobin of 10.3 g/dL, hematocrit of 30.4%, mean corpuscular volume of 85.9 fL, and platelet count of 84. Her lipase level is normal at 49 U/L. Her serum acetaminophen concentration is <3.0 mcg/mL, valproic acid level was <2 µg/mL, and she is negative for hepatitis A, B, and C. A urine toxicology screen and testing for herpes simplex, rapid plasma reagin, and human immunodeficiency virus are all negative. Results from several autoantibodies tests are negative and within normal limits, except filamentous actin (F-actin) antibody, which is slightly higher than normal at 21.4 ELISA units. Based on these results, Ms. L's liver failure seemed most likely secondary to a reaction to valproic acid.

During her pre-transplant psychiatric evaluation, Ms. L is found to be a poor historian with minimal speech production, flat affect, and clouded sensorium. She denies overdosing on her prescribed valproic acid or sertraline, reports no current suicidal ideation, and does not want to die. She accurately recalls her correct daily dosing of each medication, and verifies that she stopped taking valproic acid 2 weeks ago after being advised to do so by the ED clinicians at Visit 2. She continued to take sertraline until Visit 2. She denied any past or present episodes consistent with mania, which was consistent with her mother's report.

Ms. L becomes agitated upon further questioning, and requests immediate discharge so that she can return to her family. The evaluation is postponed briefly.

When they reconvene, the C-L team performs a decision-making capacity evaluation, which reveals that Ms. L's mood and affect are consistent with fear of her impending liver transplant and being alone and approximately 2 hours from her family. This is likely complicated by delirium due to hepatotoxicity. Further discussion between Ms. L and the multidisciplinary team focuses on the risks, benefits, adverse effects of, and alternatives to her current treatment; the possibility of needing a liver transplantation; and how to help her family with transportation to the hospital. Following the discussion, Ms. L is fully cooperative with further treatment, and the pre-transplant psychiatric evaluation is completed.

On physical examination, Ms. L is noted to have a widespread morbilliform rash covering 50% to 60% of her body.

What is the next step in management of this patient's care?

a) liver transplantation
b) L-carnitine supplementation
c) close observation

Table 3

Valproic acid formulations

Formulation	Notes
Depakote (divalproex sodium)	Delayed-release coating, cannot be crushed or chewed
Depakene (valproic acid)	Oral tablet and liquid
Depakote (divalproex sodium) extended release (ER)	Cannot be crushed or chewed
Depakote (divalproex sodium) sprinkles	Approved only for epilepsy

Source: Adapted from reference 1

The authors' observations

L-carnitine supplementation

Multiple studies have shown that supplementation with L-carnitine may increase survival from severe hepatotoxicity due to valproic acid.[8,9] Valproic acid may contribute to carnitine deficiency due to its inhibition of carnitine biosynthesis via a decrease in alpha-ketoglutarate concentration.[8] Hepatotoxicity or hyperammonemia due to valproic acid may be potentiated by a carnitine deficiency, either pre-existing or resulting from valproic acid.[8] L-carnitine supplementation has hastened the decrease of valproic acid–induced ammonemia in a dose-dependent manner,[10] and it is currently recommended in cases of valproic acid toxicity, especially in children.[8] Children at high risk for developing carnitine deficiency who need to receive valproic acid can be given carnitine supplementation.[11] It is not known whether L-carnitine is clinically effective in protecting the liver or hastening liver recovery,[8] but it is believed that it might prevent adverse effects of hepatotoxicity and hyperammonemia, especially in patients who receive long-term valproic acid therapy.[12]

TREATMENT Decompensation and transplantation

Ms. L's treatment regimen includes NAC, lactulose, and L-carnitine supplementation. During the course of Ms. L's hospital stay, her liver enzymes begin to trend downward, but her INR and PT remain elevated.

On hospital Day 6, she develops more severe symptoms of hepatic encephalopathy, with significant altered mental status and inattention. Ms. L is transferred to the ICU, intubated, and placed on the liver transplant list.

On hospital Day 9, she undergoes a liver transplantation.

What changes in Ms. L's care could have helped prevent the need for liver transplantation?

a) admission after initial elevated liver enzymes at the outside hospital (Visit 1)
b) use of psychotherapy or other behavioral methods to address Ms. L's increased anger/irritability
c) no changes could have helped prevent liver transplantation

The authors' observations

Baseline laboratory testing should have been conducted prior to initiating valproic acid. As Ms. L's symptoms worsened, better communication with her PCP and closer monitoring after starting valproic acid might have resulted in more immediate care. Early recognition of her symptoms and decompensation may have triggered earlier inpatient admission and/or transfer to a tertiary care facility for observation and treatment. Additionally, repeat laboratory testing and instructions on when to return to the ED should have been provided at Visit 1.

This case demonstrates the need for all clinicians who prescribe valproic acid to

Clinical Point

When prescribing valproic acid, remain diligent about the accurate diagnosis of mood and behavioral symptoms

Table 4

Valproic acid adverse events

Most common adverse effects (in patients with mania)	Serious adverse events
Nausea	Hepatotoxicity/DRESS syndrome
Somnolence	Pancreatitis
Dizziness	Birth defects
Vomiting	Hyperammonemia
Accidental injury	Hypothermia
Asthenia	Increased risk of suicidal ideation or behaviors
Abdominal pain	Bleeding and other hematopoietic disorders
Dyspepsia	Somnolence in older adults

DRESS: drug rash with eosinophilia and systemic symptoms

Source: Adapted from reference 1

Table 5

Suggested routine valproic acid monitoring

Time	Test
Before initiation	CBC, BMP, LFTs Weight/BMI
During titration	CBC, BMP, LFTs Valproic acid level (trough)
6 months	CBC, BMP, LFTs Weight/BMI Valproic acid level only if concern with adherence or ineffectiveness
Annually	CBC, BMP, LFTs Weight/BMI

BMI: body mass index; BMP: basic metabolic panel; CBC: complete blood count; LFTs: liver function tests

Source: Adapted from references 13,14

Clinical Point

Even after stopping valproic acid, patients who had experienced adverse events should be closely monitored to ensure complete resolution

remain diligent about the accurate diagnosis of mood and behavioral symptoms, knowing when psychotropic medications are indicated, and carefully considering and discussing even rare, potentially life-threatening adverse effects of all medications with patients.

Although rare, after starting valproic acid, a patient may experience a rapid decompensation and life-threatening illness. Ideally, clinicians should closely monitor patients after initiating valproic acid (***Table 4***[1]). Clinicians must have a clear knowledge of the recommended monitoring and indications for hospitalization and treatment when they note adverse effects such as elevated liver enzymes or transaminitis (***Table 5***[13,14]). Even after stopping valproic acid, patients who have experienced adverse events should be closely monitored to ensure complete resolution.

Consider patient-specific factors

Consider the mental state, intellectual capacity, and social support of each patient before initiating valproic acid. Its use as a mood stabilizer for "mood swings" outside of the context of bipolar disorder is questionable. Valproic acid is FDA-approved for treating bipolar disorder and seizures, but not for anger outbursts/irritability. Prior to starting valproic acid, Ms. L may have benefited from alternative nonpharmacologic treatments, such as psychotherapy, for her anger outbursts and poor coping skills. Therapeutic techniques that focused on helping her acquire better coping mechanisms may have been useful, especially because her mood symptoms did not meet criteria for bipolar disorder, and her depression had long been controlled with sertraline monotherapy.

OUTCOME Discharged after 20 days

Ms. L stays in the hospital for 10 days after receiving her liver transplant. She has low

appetite and some difficulty with sleep after the transplant; therefore, the C-L team recommends mirtazapine, 15 mg/d. She has no behavioral problems during her stay, and is set up with home health, case management, and psychiatry follow-up. On hospital Day 20, she is discharged.

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Related Resource

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Drug Brand Names

Diphenhydramine • Benadryl
Famotidine • Fluxid, Pepcid
Lamotrigine • Lamictal
Mirtazapine • Remeron
N-acetylcysteine • Mucomyst
Phenobarbital • Luminal
Phenytoin • Dilantin
Prednisone • Cortan, Deltasone
Sertraline • Zoloft
Valproic acid • Depakene

Clinical Point

Prior to starting valproic acid, Ms. L may have benefited from nonpharmacologic treatments for her anger outbursts

Bottom Line

Use caution when prescribing valproic acid, even in young, otherwise healthy patients. Although rare, some patients may experience a rapid decompensation and life-threatening illness after starting valproic acid. When prescribing valproic acid, ensure close follow-up after initiation, including mental status examinations, physical examinations, and laboratory testing.