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Death Delusions and Myoclonus: Acyclovir Toxicity

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PRESENTATION

The therapies we administer often have the potential to trigger severe adverse reactions; particularly in patients with compromised organ function. For that reason, it is essential to be familiar with clinical syndromes spurred by drug toxicity and to include them in the differential diagnosis. Recognition of a life-threatening reaction was crucial when a 65-year-old woman with end-stage renal disease presented with peculiar signs and symptoms.

As an outpatient, she was diagnosed with a multidermatomal herpes zoster infection (Figure 1) and prescribed valacyclovir, 1 gram every 8 hours, with prednisone. The next day, the patient began to hallucinate, asking, "Who is going to die? Me or that guy?" In addition, she exhibited emotional lability and agitation. She was taken to an urgent care center, where it was determined that her symptoms were secondary to steroid-induced psychosis. The prednisone was discontinued. Yet, her neuropsychiatric symptoms worsened over the next 24 hours. Ultimately, she became less alert and was unable to respond appropriately to questions. She was brought to the emergency department for further evaluation.

ASSESSMENT

Upon presentation to the emergency department, the patient's Glasgow Coma Scale was 10 (eye response, 3; verbal response, 2; motor response, 5). Her temperature was 101.1°F (38.4°C), blood pressure was 192/84 mm Hg, heart rate was 113 beats per minute, and she had an oxygen saturation of 100% on 4 liters of oxygen by nasal cannula. The patient was visibly agitated and did not respond to questions. She had no nuchal rigidity. In the C2-C5 dermatomal distribution on the right, she had an extensive vesicular, erythematous eruption in various stages of healing (Figure 1). She had no other rashes present, but she did have diffuse pulmonary crackles without wheezing and tachycardia without murmurs. On neurologic examination, myoclonus was present in her extremities, all reflexes were symmetric without clonus, and her toes were downgoing.

Concerns for herpetic encephalopathy led to computed tomography of the patient's brain. The results were negative for an acute intracranial process, and a lumbar puncture was performed, with results as detailed in Table 1. Empiric intravenous vancomycin, ceftriaxone, and acyclovir (1 gram) were administered. A chest radiograph demonstrated pulmonary edema. An electrocardiogram showed sinus tachycardia with lateral ST depression and inferior T-wave inversion secondary to demand-induced ischemia. A bedside electroencephalogram disclosed diffuse slowing.

The remaining peripheral blood laboratory evaluation identified hemoglobin of 12.1 mg/dL, leukocytosis at 13.1×10^9 cells/mm^3 (82% segmented neutrophils, 10% lymphocytes, and 1% bands), and a platelet count of 197,000 platelets/μL. Her chemistry panel was unchanged from baseline measurements. Results from a liver function panel, urine and blood drug screens, rapid plasma reagin test, thyroid-stimulating hormone test, lactate dehydrogenase test, and a haptoglobin blood test were all within normal limits.

DIAGNOSIS

Given our patient's specific presentation and the benign results of the lumbar puncture, acyclovir-induced neurotoxicity was strongly suspected. Presenting symptoms are neuropsychiatric and include disturbances in consciousness, myoclonus, seizures, coma, and death delusions. Most commonly, patients have had a preceding herpes zoster infection that has been treated with dosages of oral acyclovir or valacyclovir that were not properly calculated based on

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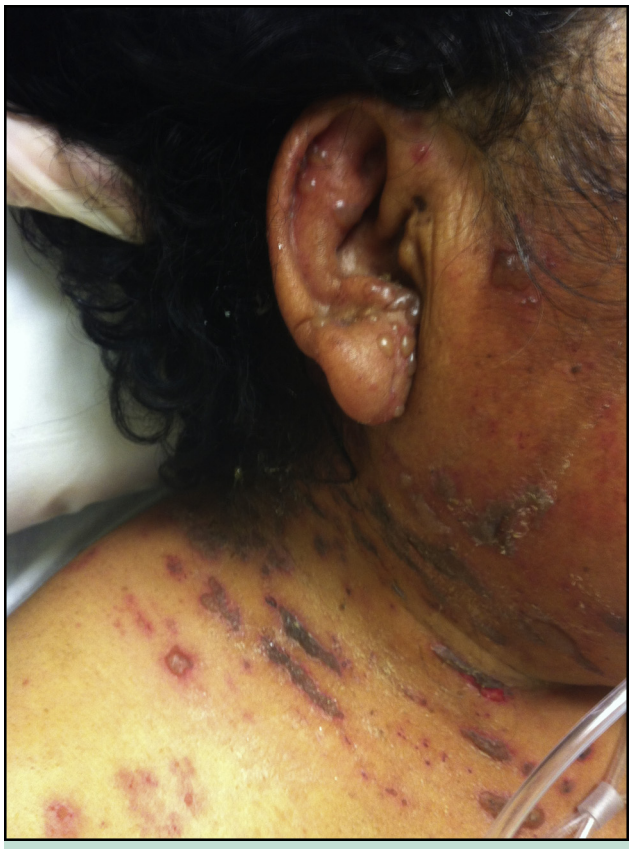

Figure 1 The patient had herpes zoster infection with extensive vesicular, erythematous eruptions in various stages of healing in the C2-C5 dermatomal distribution on the right.

their level of renal dysfunction. Symptoms typically occur after the third or fourth dose and are rapidly progressive, especially if drug administration continues.[1]

Acyclovir-induced neurotoxicity must be accurately diagnosed, and mainly, it must be distinguished from herpes encephalitis, as treatments for the 2 disorders are discordant. Patient history, symptom profiles, and lumbar puncture results can combine to provide reliable differentiation. Hallucinations, death delusions, and involuntary movement are more specific for acyclovir toxicity.[1] In contrast, high fever, headaches, and seizures, while nonspecific, are more indicative of herpes encephalitis.[2]

Table 1 Cerebrospinal Fluid Results

	Tube #1	Tube #4
Color	Colorless	Clear
Clarity	Colorless	Clear
Nucleated cells	2 per cm^3	2 per cm^3
RBCs	1 per cm^3	4 per cm^3
Protein	41 mg/dL	
Glucose	115 mg/dL (Serum 223 mg/dL)	

RBCs = red blood cells.

Once acyclovir-induced neurotoxicity is suspected, the diagnosis can be confirmed by identifying elevated cerebrospinal fluid levels of the acyclovir metabolite 9-carboxymethoxymethylguanine (9-CMMG).[3,4] Valacyclovir (a prodrug) is hydrolyzed via first-pass metabolism to acyclovir, which is excreted primarily unchanged in the urine. The small percentage of acyclovir that is not eliminated unchanged is oxidized sequentially to 9-CMMG and to a very minor metabolite, 8-hydroxy-acyclovir.[5] Patients with impaired renal function are vulnerable to drug toxicity due to their compromised ability to eliminate the unchanged acyclovir through the urine. Therefore, its half-life is increased from 2-3 hours in patients with normal renal function to 14 hours in patients with end-stage renal disease—a situation leading to stacking of doses and subsequent drug accumulation.[3,4]

In addition, transporting proteins in the blood-brain and blood-cerebrospinal fluid barriers, which control movement of compounds from the blood to the brain and cerebrospinal fluid, respectively, and vice versa, may be inhibited by acyclovir or its metabolites.[6] Thus, it is believed that as serum acyclovir and its metabolites, including 9-CMMG, increase to toxic levels, they may continue to cross these barriers and gain access to the brain with proportionately decreased metabolism and clearance out of the cerebrospinal fluid. Although cerebrospinal fluid levels of acyclovir poorly correlate with development of neuropsychiatric symptoms, levels of 9-CMMG in the cerebrospinal fluid have been found to strongly correlate with the severity of neuropsychiatric symptoms.[3,7] In our patient, confirmatory testing of acyclovir-induced neurotoxicity was performed using serum and cerebrospinal fluid samples. These revealed an elevated level of 9-CMMG (1.03 mcg/mL) in the cerebrospinal fluid, an amount 4.5 times greater than the median drug level (0.22 mcg/mL) at which neuropsychiatric symptoms are seen.[3]

Interestingly, the finding of "le délire des négations," or the delirium of negation—the patient's conviction that he or she is dead—was originally described by Dr. Jules Cotard, a 19th-century French neurologist. More commonly known as Cotard's syndrome, death delusions have been described as a more specific symptom seen in acyclovir neurotoxicity.[8] A case series of 275 patients diagnosed with acyclovir-induced neurotoxicity described depression and suicidal ideations in 5% of patients.[6] These findings highlight the psychiatric component of the neuropsychiatric symptoms.

MANAGEMENT

Once the diagnosis of acyclovir-induced neurotoxicity is made, treatment consists of immediate discontinuation of the offending agent and hemodialysis. Further doses of acyclovir were withheld from our patient. A nephrology consultation resulted in a recommendation for immediate dialysis, and this was performed in 6-hour sessions on 3 consecutive days. On the evening following the second dialysis session, the patient showed significant improvement

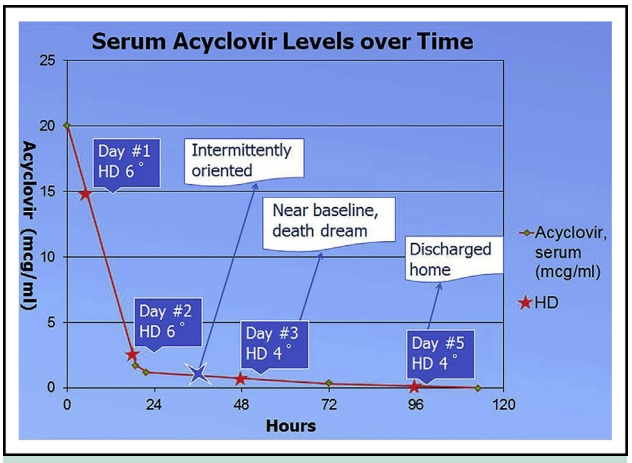

Figure 2 The patient's serum acyclovir levels during her hospital course are shown. These were significantly reduced after the first 2 sessions of hemodialysis.

in her mental status and was able to communicate clearly, including being oriented to name, place, and loosely, to her situation. On hospital day 3, her alertness improved enough that she was able to pass a bedside swallow examination. The patient's daughter felt she was nearly back to baseline but reported that during the evening between hospital days 3 and 4, the patient had dreamed that the world was ending. By hospital day 5, the patient returned to her cognitive and functional baseline status and was discharged home to resume her usual outpatient hemodialysis schedule.

As seen in **Figure 2**, serum acyclovir levels significantly dropped after the first 2 sessions of hemodialysis. However, her symptoms persisted for at least another day, a finding consistent with the notion that serum acyclovir levels poorly correlate with the presence of neuropsychiatric symptoms. Other authors have found that although a 3-4 hour dialysis session reduces serum levels of 9-CMMG and acyclovir levels by 64% and 58%, respectively, several sessions are required for resolution of symptoms in severe cases of acyclovir-induced neurotoxicity.[4]

CONCLUSION

Patients with a recent history of herpes zoster infection and underlying chronic kidney disease are the patient population most vulnerable to develop acyclovir-induced neurotoxicity. Renal impairment demands dosage adjustments of antiviral therapy to prevent potentially fatal drug toxicity (**Table 2**).[9] Altered mental status in the setting of acyclovir or valacyclovir use for herpes zoster infection can suggest either drug toxicity or viral encephalitis, but certain symptoms have

Table 2 Recommended Valacyclovir Dosing[9]

GFR (mL/min)	Dosing
50	1000 mg q 8H × 7 days
30-49	1000 mg q 12H
10-29	1000 mg q 24H
<10	500 mg q 24H
Hemodialysis	500 mg post hemodialysis

GFR = glomerular filtration rate; q = every; H = hours.

increased specificity for toxicity. These include myoclonus and neuropsychiatric symptoms, such as death delusions and depression. Together, recognition of these symptoms, accurate medication reconciliation, and assessment of clinical context—especially, identification of the risk factor of renal insufficiency—result in prompt recognition of drug toxicity, early initiation of treatment, and improved clinical outcomes. Since 9-CMMG testing has very limited availability, clinical recognition of acyclovir toxicity is essential. This case underscores the importance of careful prescribing in renal failure patients.

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