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NEUROLOGIC ACYCLOVIR TOXICITY IN THE ABSENCE OF KIDNEY INJURY

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□ **Abstract—Background: Herpes zoster (zoster) also commonly known as "shingles," occurs following reactivation of the varicella zoster virus. It contributes a large cost burden to the U.S. health care system, with an estimated 1 million cases costing $1 billion annually. The current gold standard treatment is acyclovir, which limits viral replication. However, acyclovir has been reported to cause neurotoxicity in patients with acute or chronic kidney disease. Case Report: This case presents an occurrence of acyclovir-induced toxic encephalopathy in a patient with normal renal function. A 63-year-old male presented to the emergency department with ataxia, tremors, fluctuating aphasia, confusion, agitation, and fatigue. Results of imaging, lumbar puncture, and laboratory studies directed clinicians toward acyclovir toxicity, despite a normal creatinine level. Why Should an Emergency Physician Be Aware of This?: Emergency physicians will likely be the first point of contact in the health care system following the onset of acyclovir toxicity. With an increasing incidence of zoster disease, such atypical toxic manifestations may increase. Early recognition is important to avoid permanent neurologic compromise.**

□ **Keywords—acyclovir toxicity; encephalopathy; varicella zoster virus; renal function**

INTRODUCTION

We report a case of encephalopathy due to acyclovir in a patient who had herpes zoster (zoster) but who did not have any prior evidence of renal dysfunction. Acyclovir is known to occasionally cause encephalitis in patients with renal dysfunction, but our patient lacked this risk factor.

Acyclovir is a nucleoside analog that is currently used to limit replication of multiple viruses, including herpes simplex virus, cytomegalovirus, and varicella zoster virus (VZV). Of people born in the United States, 99.5% aged older than 40 years have been infected with VZV. Reactivation of VZV results in zoster, with an estimated incidence of 1 million. The rate of VZV has been rising steadily. As a result, the number of acyclovir prescriptions are believed to have also increased (1–3).

Acyclovir has a high volume of distribution within the body, allowing it to penetrate widely, including the cerebrospinal fluid. The drug is mainly eliminated by the kidneys, therefore, in the presence of kidney injury, levels may rise, causing subsequent development of neurotoxicity (4). Patients suffering from toxicity often present with tremors, myoclonus, confusion, lethargy, and agitation (4). Importantly, this case highlights that acyclovir toxicity can also develop in patients with normal kidney function. In this report, we emphasize the importance of recognizing key clinical signs of acyclovir toxicity in patients with normal renal function. Awareness of such adverse reactions in the setting of normal kidney function will help avoid precipitation of severe toxicity consequences. Three antivirals are commonly used to treat zoster, including famciclovir, valacyclovir, and acyclovir.

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Post-marketing surveillance, based on case reports, estimates neurotoxicity incidence is <1% for all three drugs (5–7). All three have associated reports of neurotoxicity in patients with decreased renal function (4,8–12). Only one case of neurotoxicity could be identified in the literature in a patient without prior kidney disease, however, the patient, who was taking valacyclovir, presented with acute kidney injury (AKI) (12). We describe the unique case of a patient who developed acyclovir neurotoxicity despite having normal renal function.

CASE REPORT

A 63-year-old male presented to the emergency department with complaints of 5 days of fatigue and the development of confusion within the past 24 h. The patient's history was significant for coronary artery disease, hyperlipidemia, and gout. He had been diagnosed with zoster 5 days prior, and was treated with acyclovir 800 mg five times daily since the date of diagnosis.

On initial examination, the patient had a heart rate of 108 beats/min, a respiratory rate of 18 breaths/min, a temperature of 36.8°C, and a blood pressure of 189/114 mm Hg. No nuchal rigidity or lateralizing neurologic deficits were identified, and cranial nerves II–XII were grossly intact. Intention tremors, ataxia, and fluctuating receptive and expressive aphasia were noted. Evidence of VZV infection was visualized as a T4–T5 dermatomal rash on his left back and chest wall.

Laboratory values were significant for mildly elevated blood glucose, aspartate aminotransferase, and alanine aminotransferase, and a normal white blood cell count, creatinine, ammonia, and troponin (Table 1). An electrocardiogram demonstrated a normal sinus rhythm and no acute ischemic changes. Magnetic resonance imaging (MRI) of the brain was attempted, but due to agitation, a computed tomography (CT) scan without contrast was performed, which demonstrated no acute hemorrhage or signs of ischemia. The patient was empirically treated with i.v. acyclovir for the possibility of herpes simplex virus encephalitis, as well as ceftriaxone and vancomycin for the possibility of acute bacterial meningitis.

The patient was then admitted to the intensive care unit (ICU) due to concerns about further deterioration in his mental status. With continued agitation, the patient was intubated to safely obtain an MRI of his brain and complete a lumbar puncture for cerebral spinal fluid (CSF) analysis. The MRI was negative for evidence of an acute infarction, hemorrhage, edema, or mass effect. The CSF analysis was not consistent with a bacterial or viral etiology (Table 1). An electroencephalogram (EEG) showed diffuse slow wave abnormality consistent with mild to moderate generalized encephalopathy and a few frontal sharp waves consistent with interictal expression of epileptiform discharges, but no evidence of status epilepticus or electrographic seizures. The antibiotics and acyclovir were discontinued.

On day 2 of his ICU admission, the patient's mental status began to clear, and he was extubated. Based on his history, imaging, laboratory results, and discussion between the intensivist and neurologist, it was concluded that the patient had developed acute acyclovir neurotoxicity. By day 6 of his admission to the hospital, the patient had returned to his baseline, mentally and physically, and was discharged.

DISCUSSION

Acute onset of neurologic symptoms in patients being actively treated for zoster merits the consideration of acyclovir toxicity in the differential diagnosis. In this case, the patient presented with acute generalized weakness, fatigue, global ataxia, intention tremors, confusion, and agitation. These symptoms align with previous reports of acyclovir neurotoxicity. However, the development of this complication has only been reported in patients with clear signs of renal dysfunction.

The non-focal symptoms in association with intention tremors displayed by our patient raised suspicion for toxicity or encephalitis/meningitis more than an ischemic stroke. However, it is important to rule out vascular causes of acute neurologic symptoms. CT and MRI studies showed no acute pathology that would suggest a stroke. To distinguish encephalitis from acyclovir toxicity, a lumbar puncture is essential. For the diagnosis of central nervous system infections due to VZV, polymerase chain reaction (PCR) and VZV antibody synthesis both have 100% sensitivity. Pleocytosis is seen in 94% of cases, and patients are also often febrile (13). The lumbar puncture of our afebrile patient did not show marked pleocytosis and viral PCR studies were negative, raising the suspicion for a neurotoxicity etiology. The EEG tracing showed characteristic sharp spikes with a general slowing, indicating an increased risk for seizure activity, but no ongoing current seizure activity to explain the encephalopathy. The acute onset of the patient's neurologic symptoms, followed by their rapid resolution immediately after discontinuation of the acyclovir in the context of a negative infectious evaluation (Table 1), suggested the etiology for the patient's symptoms was due to acyclovir toxicity.

There are several situations that can lead to the development of acyclovir toxicity. Efficacious acyclovir levels in the serum are between 9 and 18 μg/mL and are below the neurotoxic threshold for acyclovir (14). Due to the high volume of distribution of acyclovir, patients with decreased muscle mass as a consequence of aging or

Table 1. Pertinent Laboratory Results With Reference Ranges

Test	Component	Result	Reference Range	Units
Complete blood count	WBCs	7.1	4.5–11.0	1000/μL
	Hemoglobin	16.1	13.0–17.0	g/dL
	Platelets	305	150–400	1000/μL
Comprehensive metabolic panel	Sodium	135	135–145	mmol/L
	Potassium	4	3.5–5.1	mmol/L
	Bicarbonate	22	22–32	mmol/L
	Anion gap	13	4.0–17.0	mmol/L
	Glucose	113	70–99	mg/dL
	Creatinine	1.2	0.4–1.2	mg/dL
	GFR	> 60	≥ 61	mL/min
	Calcium	9.1	8.4–10.5	mg/dL
	Total protein	8.1	6.1–7.9	g/dL
	Alkaline phosphatase	88	30–96	IU/L
	Aspartate aminotransferase	46	15–41	IU/L
	Alanine aminotransferase	61	5.0–40	IU/L
	Bilirubin total	1.2	0.0–1.2	mg/dL
Ammonia	—	21	9.0–35	μmol/L
Troponin	—	< 0.03	0.0–4.0	ng/mL
Procalcitonin	—	0.06	0.5–2.0	ng/mL
Urinalysis	Nitrite	Negative	Negative	—
	Luekocyte esterase	Negative	Negative	—
	WBCs	0	0–4	HPF
	Bacteria	Negative	Negative	—
Urine drug screen	Amphetamine	Negative	Negative	—
	Barbiturate	Negative	Negative	—
	Benzodiazepine	Positive	Negative	—
	Buprenorphine	Negative	Negative	—
	Cannabinoid	Negative	Negative	—
	Cocaine	Negative	Negative	—
	Ecstasy	Negative	Negative	—
	Ethanol	Negative	Negative	—
	Opiates	Negative	Negative	—
Cerebral spinal fluid analysis	Color	Colorless, pink	—	—
	RBCs	3950	0	cells/μL
	WBCs	17	0–5	cells/μL
	Polynuclear	89	0	%
	Mononuclear	11	100	%
	Glucose	60	40–70	ng/dL
	Protein	47	15–45	mg/dL
	Gram stain	No bacteria	—	—
	Herpes virus PCR	Negative	—	—
	Varicella zoster PCR	Negative	—	—
	Haemophilus influenza Ag	Negative	—	—
	Neisseria meningitidis Ag	Negative	—	—
	Streptococcus pneumoniae Ag	Negative	—	—
	Strep Group B Ag	Negative	—	—

GFR = glomerular filtration rate; HPF = high power field; PCR = polymerase chain reaction; RBC = red blood cell; WBC = white blood cell.

other conditions may have higher serum levels of drug than intended. Fluid intake may also play a role, as decreased intravascular volume can theoretically decrease renal clearance of renally excreted compounds. The exact mechanism for acyclovir-induced neurotoxicity remains unclear (15). Despite appropriate dosing, our 63-year-old patient developed manifestations of acyclovir neurotoxicity in the absence of kidney disease. A serum acyclovir level was not obtained for our patient, as the laboratory would have been sent out with a 2- to 3-week turnaround time, preventing use of this measurement during the acute management period. Overall, the routine testing of serum acyclovir levels in cases of suspected acyclovir toxicity has not been found to be uniformly helpful (14,16).

Both the RIFLE (Risk, Injury, Failure, Loss of Kidney Function and End-Stage Kidney Disease) and AKIN (Acute Kidney Injury Network) criteria indicated that our patient had no evidence of AKI on admission, using his baseline creatinine of 1.0 mg/dL (17–19). His creatinine upon admission was 1.2 mg/dL, which is at the upper reference limit of normal. Nonetheless, perhaps a standalone creatinine of 1.2 mg/dL, as seen in this patient, may warrant suspicion for impending toxic accumulation of acyclovir, as his creatinine trended down to 0.9 mg/dL during his hospitalization. This may reflect

a pre-renal azotemia due to hypovolemia and a reduction in glomerular filtration rate (GFR) around the time of toxicity development. It is unknown whether his creatinine was > 1.2 mg/dL within the week prior to his admission.

Consideration of acyclovir toxicity was initially deterred because patients typically present with acute or chronic kidney disease (11). A serious but rare complication of acyclovir is AKI, which can develop following acyclovir crystal deposition in the renal tubules (20). However, a risk assessment for AKI in patients on acyclovir indicated this is a rare occurrence, as patients on acyclovir had minimal risk of developing AKI when compared to famciclovir, a drug with no known renal toxicity (20). This was not suspected to be the case for our patient, based upon his normal kidney function.

Dosing for acyclovir depends on immunocompetency and GFR. All patients with reported acyclovir neurotoxicity in the literature have had prior or acute kidney disease (8–10,16). Lack of renal toxicity may be why there are fewer reports of famciclovir neurotoxicity and none in patients with normal GFR. All reports of acyclovir neurotoxicity have occurred in patients with decreased GFR (8–10,16). Valacyclovir has been reported to have neurotoxicity in patients with decreased GFR on multiple occasions (8,10,11). In the 2018 report by Yoshimura et al., valacyclovir neurotoxicity occurred in a patient without prior kidney disease, but AKI was present on admission (12). This case is novel in presenting an occurrence of acyclovir toxicity in a patient with no prior kidney disease and no AKI on presentation. Of the antiviral treatment options available for zoster (acyclovir, valacyclovir, and famciclovir), acyclovir remains the most effective in terms of resolving zoster (21). However, when attempting to avoid neurotoxicity in susceptible patients, such as the elderly, famciclovir may be superior due to fewer reports of neurotoxicity in literature and lack of nephrotoxicity.

In immunocompromised patients with disseminated zoster, VZV encephalitis may develop, and empirical i.v. acyclovir is standard treatment. In hindsight, for this patient with current neurologic symptoms from oral acyclovir, a switch to i.v. acyclovir increased the bioavailability of the drug, and could have intensified the neurologic symptoms, as seen in other previously published cases of acyclovir toxicity (8–10,16). Prompt CT/MRI, followed by lumbar puncture, can rule out VZV encephalitis and other potential infectious etiologies of the altered mental status, allowing prompt discontinuation of acyclovir. It is essential to avoid worsening neurologic function associated with acyclovir toxicity, as one case in the literature reported permanent paresthesias (22). Other significant sequelae include status epilepticus, which in itself is associated with greater mortality, poor functional outcomes, and epileptogenesis (23). Prompt investigation and diagnosis of acyclovir toxicity will help avoid these more severe outcomes.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

Due to the rapid onset, individuals with acute acyclovir toxicity or severe altered neurologic symptoms will first report to the emergency department for care. As rates of VZV rise, clinicians should be aware of the potential for acyclovir toxicity presenting with neurologic symptoms in patients with adequate kidney function. Key acute, non-focal symptoms in the absence of positive imaging, lumbar puncture, and viral studies should increase suspicion of this toxicity. Rapid recognition, diagnosis, and treatment of acyclovir toxicity will reduce the chances of permanent neurologic sequelae.

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