Case Report

An Unusual Neurological Syndrome in a Haemodialysis Patient

Abstract

Advanced age and immunosuppressed states allow for complications of herpes zoster such as encephalitis. In this case report, we describe a patient with encephalopathy two days after initiation of antiviral therapy. After the necessary imaging and cerebrospinal fluid (CSF) analysis, it became evident that the neurological syndrome was due to acyclovir. Despite currently practised renal dose modification, the patient developed acyclovir-induced neurotoxicity and required intensification of his dialysis schedule to eliminate the drug. Acyclovir-induced neurotoxicity is a rare clinical presentation and presents a clinical dilemma to the physician who has to distinguish this entity from herpes zoster encephalitis and posterior circulation stroke.

Keywords: *Acyclovir, encephalopathy, herpes zoster, dose adjustment*

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Introduction

Herpes zoster is a common problem with an incidence of 3-4 cases per 1000 people per year.[1] Incidence increases with increasing age. Chronic kidney disease (CKD) is an immunosuppressed state allowing flares of herpes zoster. The altered sensorium in the setting of a zoster patient could represent encephalopathy due to the virus or drug toxicity. These represent opposite ends of the spectrum requiring entirely contradictory treatment paths. Hence, the importance of defining these entities and distinguishing between them need to be emphasized. Acyclovir toxicity in the setting of CKD leading to encephalopathy has been described in very few cases of herpes zoster across the world and one case with valacyclovir-induced neurotoxicity in a hemodialysis patient had been previously described from India.[2] This case report highlights the salient clinical features and clinical course of acyclovir-induced encephalopathy (AIE) in a dialysis patient.

Case Presentation

A 65-year-old gentleman who was on twice weekly dialysis presented with a history of vesicular rash in the thoracic dermatome for 2 days. He was a known diabetic and hypertensive and had developed end-stage renal disease due to diabetes. His dialysis vintage was 4 months. He was also on the maintenance phase of antituberculous therapy, which included isoniazid and rifampicin for pulmonary tuberculosis. He was conscious, oriented, was able to give history coherently. In view of advanced age and immunosuppressed state, he was prescribed acyclovir at a dose of 400 mg thrice daily.

Two days after the initiation of acyclovir, he was brought into the emergency department with dysarthria, drowsiness, and disorientation. His blood pressure on arrival was 150/90 mm Hg. Neurological evaluation revealed cerebellar signs such as past pointing and rebound in bilateral upper limbs along with slow speech. The rash of herpes zoster exhibited crusting. The differential diagnoses considered at this time were posterior circulation stroke, herpes zoster encephalitis, acyclovir toxicity, isoniazid psychosis, and metabolic or septic encephalopathy. Except for low hemoglobin (9.5 g/dl) and increased urea and serum creatinine, rest of the biochemistry was normal. Magnetic resonance imaging (MRI) brain was normal with only age-related cerebral atrophy. Intravenous acyclovir at a dose of 5 mg/kg once daily was started empirically.

Blood culture showed no growth. Cerebrospinal fluid (CSF) analysis showed no evidence of pus cells [Table 1]. Quantitative polymerase chain

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Table 1: Cerebrospinal fluid analysis of a patient with VZV

CSF Laboratory analysis	Report of test
WBC count	NIL
RBC count	NIL
Protein	65.3 mg/dl
Glucose	50 mg/dl
Adenosine Deaminase (ADA)	1.9 IU/L
Appearance	Straw color
Quantitative VZV Panel PCR	negative
Viral encephalitis PCR panel	
EBV	negative
CMV	negative
Adenovirus	negative
HSV1	negative
HSV2	negative
WNV	negative
EV	negative
JEV-	negative
Bacterial Culture	negative
Fungal Culture	negative
X-pert -TB PCR	negative
Cytology CSF	Negative

CSF: Cerebrospinal fluid; TB PCR: tuberculosis polymerase chain reaction; JEV: Japanese encephalitis virus; HSV1: herpes simplex virus 1; EV: Enterovirus; WNV: West Nile virus; CMV: Cytomegalovirus; EBV: Epstein-Barr virus; VZV: Varicella Zoster Viral; WBC: white blood cell; RBC: red blood cell

reaction (PCR) for the Varicella zoster virus was negative. To rule out other causes of viral encephalitis endemic to the region, multiplex PCR analysis was done. Bacterial, fungal and tuberculous cultures, as well as cytology of CSF, were done and negative [Table 1]. The diagnosis of probable acyclovir-induced encephalopathy was made and the patient was given frequent sittings of hemodialysis to remove the drug along with stopping the medication. Within three days, his sensorium showed gradual improvement and cerebellar signs regressed and over the next couple of days, his sensorium normalized.

Discussion

Herpes zoster is a common entity among the elderly population with an incidence of 1 million cases per year in the US.[3] Uremic patients have defective innate and adaptive immunity. It has been noted that patients on hemodialysis have an increased risk of varicella-zoster virus (VZV) infections compared to the general population.[4] Risk factors for cranial herpes infection include dissemination and immunosuppression. Tremors and disorientation are the most common clinical manifestations, seen in 40% of people each, while agitation and hallucinations are seen in 22 and 25% of cases, respectively.[5] Hallucinations, death delusions, and involuntary movements are features that are specific of toxicity due to acyclovir. In comparison, high fever, headache, and seizures are more suggestive of encephalitis.[6] Cutaneous herpes and cranial herpes usually do not occur concomitantly. Median duration of 15 days between the two in immunosuppressed and 5 days in immunocompetent patients have been previously described.[5] Individuals over 50 years and immunocompromised individuals require antiviral therapy for the treatment of herpes zoster lesions.

Acyclovir is commonly prescribed for herpes zoster and is cost-effective. Acyclovir was first developed in 1974. Its oral bioavailability is only about 10-30%. About 60-90% of the drug undergoes renal elimination through filtration and secretion. About 9-33% is protein bound.[7] In those with renal failure, there is a linear increase in acyclovir levels as renal function declines with a predicted intercept value of 28.7 ml/min/1.73 m.[8] This is the rate of acyclovir clearance in anuric patients and this value is used to calculate renal dose adjustment of acyclovir.

There are no typical imaging findings of AIE. Some case reports have described multifocal white matter signal intensities in the cerebellum, pons and periventricular region. There is also one reported case of posterior leukoencephalopathy due to acyclovir in literature.[9] Our patient did not have any abnormal imaging findings.

Plasma levels of acyclovir can be checked using high -performance liquid chromatography or radioimmunoassay. 9-Carboxymethoxy methylguanine (CMMG), the active metabolite of acyclovir can be measured from serum or CSF. High levels seem to correlate well with neurotoxicity. This assay is only available at few centers and is not routinely done for diagnosis. A study by Helleden *et al*. showed that CMMG levels have a sensitivity of 91% and specificity of 93% for the development of neuropsychiatric symptoms.[10] Acyclovir levels have shown a poor correlation with clinical recovery. Despite the rapid fall of acyclovir levels after drug removal through dialysis, clinical response is not rapid. This is probably explained by slow equilibration between blood and brain levels of the drug. In our opinion, the routine measurement of acyclovir levels to determine neurotoxicity is not required.

In those with renal failure, dose is adjusted in a stepwise manner according to the glomerular filtration rate (GFR). Despite following manufacturers' available renal adjustment, in a study by Kransy *et al*., acyclovir levels were are two times the upper limit of normal in the CSF than that in patients with normal renal function.[11] This call into question the precision of our currently available renal dose adjustment system? Perhaps the renal adjustment needs to decrease doses further to maintain therapeutic targets but maintain drug efficacy.

Treatment of AIE involves dialysis for drug removal. Within 48-72 hours there is usually improvement of symptoms. Still, other authors have suggested a therapeutic trial of hemodialysis as a means to diagnose AIE in patients who are encephalopathic where it is difficult to distinguish between

zoster-related encephalitis and AIE.[12] In the study by Kransky *et al*., the extraction ratio of acyclovir for each dialysis session was found to be 0.45 ± 12. Since then more efficient dialyzers have evolved and with better blood and dialysate flow, up to 45%, of removal from a single 3-hour dialysis session has been reported by Leiken *et al*.[13] Experience with peritoneal dialysis for acyclovir removal is limited and it was found to eliminate only 10% of the total drug dose.[14]

The diagnosis of acyclovir-induced neurotoxicity hinges on the temporal profile of toxicity developing within 72 hours of exposure to acyclovir in the absence of other clinical and laboratory features that are typical of herpes zoster encephalitis and improvement with drug withdrawal and/or removal through dialysis.

No doubt, herpes zoster lesion should be treated keeping in mind the patient's age and immunosuppressed state. But does the dose currently prescribed need amendment? Existing renal drug dosage schedules are not precise and have currently lead to case reports of neurotoxicity and excessive levels of acyclovir or its active metabolite even when the drug is administered in recommended doses. Should we have used intravenous acyclovir at 2.5 mg/kg body weight? In the medical literature, no pharmacokinetic studies on acyclovir levels in renal failure patients are available after 1980s. Further research on appropriate drug dosage and recommendations from professional bodies are well overdue.

Conclusions

Encephalopathy in a hemodialysis patient should be approached diligently. Even with the currently prescribed Renal adjusted acyclovir dose, drug toxicity can occur. Newer pharmacokinetic studies on acyclovir and other commonly prescribed drugs in renal failure patients are recommended.

Declaration of consent

The authors confirm that the patient consent was obtained and all efforts to maintain anonymity were followed although anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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