

Valacyclovir-Associated Neurotoxicity Presenting as Acute Encephalopathy in an Elderly Hemodialysis Patient: A Case Report



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ABSTRACT

Valacyclovir-associated neurotoxicity (VAN) is a recognized adverse effect in elderly patients with renal impairment but remains underdiagnosed due to its nonspecific presentation and overlap with acute neurologic emergencies. We report a 78-year-old Filipino female with end-stage renal disease on maintenance hemodialysis who developed acute disorientation, agitation, vivid visual hallucinations and generalized weakness shortly after initiation of valacyclovir for herpes zoster. Given the abrupt onset of neuropsychiatric symptoms, viral encephalitis was initially considered. Magnetic resonance imaging of the brain showed no evidence of acute infarction or encephalitis, while electroencephalography demonstrated diffuse generalized slowing consistent with an encephalopathic process. Review of the medication history revealed valacyclovir dosing that exceeded recommendations for patients with end-stage renal disease. Valacyclovir was discontinued

and emergent hemodialysis was initiated resulting in marked improvement in sensorium after the second session and complete resolution of symptoms after the third. This case shows VAN as an important diagnostic mimic of acute encephalopathy in elderly patients with renal failure and emphasizes the critical role of early medication review in preventing unnecessary investigations and enabling prompt, reversible management.

Key Words: Valacyclovir-associated neurotoxicity, Hemodialysis, Elderly patient, Renal impairment, Herpes zoster

INTRODUCTION

Valacyclovir is a commonly prescribed antiviral agent for herpes virus infections because of its favorable oral bioavailability and safety profile. However, valacyclovir-associated neurotoxicity (VAN) is a recognized adverse effect, particularly in elderly patients and those with renal impairment in whom impaired drug clearance leads to accumulation of neurotoxic metabolites.[1–3] Despite increasing recognition, VAN remains underdiagnosed in routine clinical practice.

The clinical presentation of VAN is often nonspecific, ranging from confusion and agitation to hallucinations and encephalopathy, and may closely mimic acute neurologic emergencies such as viral encephalitis or stroke.[2-4] Neuroimaging is

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frequently unremarkable and electroencephalography typically shows nonspecific generalized slowing, contributing to diagnostic uncertainty.[2,5] Patients with end-stage renal disease are particularly vulnerable due to prolonged acyclovir half-life and increased exposure to its neurotoxic metabolite, 9-carboxymethoxymethylguanine (CMMG).[6,7]

In this report, we describe a 78-year-old Filipino female with end-stage renal disease on maintenance hemodialysis who developed acute neuropsychiatric symptoms mimicking viral encephalitis after valacyclovir therapy, showing the importance of early medication review to prevent unnecessary investigations and facilitate prompt, reversible management.[3,8]

CASE REPORT

A 78-year-old Filipino female with a history of hypertension, diabetes mellitus and end-stage renal disease on maintenance hemodialysis three times weekly presented with a four-day history of painful and pruritic vesicular lesions over the left postauricular area extending to the anterior neck. She was evaluated by an internist and clinically diagnosed with herpes zoster involving the C3 dermatome. Valacyclovir was initiated at a dose of 1 g three times daily.

After the second dose of valacyclovir, the patient developed sudden-onset disorientation, agitation, vivid visual hallucinations and generalized body weakness, prompting consultation at the emergency department. On arrival, her vital signs were stable. Neurologic examination revealed an irritable and disoriented patient who reported seeing Caucasian children running around, as well as floating animals and fruits. Motor examination showed generalized limb weakness with a Medical Research Council (MRC) grade of 3/5, without focal asymmetry. There were no cranial nerve deficits, pathologic reflexes, extensor plantar responses, or signs of meningeal irritation.

Initial laboratory investigations revealed normal complete blood count, platelet count, serum sodium, serum phosphate and fasting blood glucose levels. Serum potassium was elevated at 6.7 mEq/L. Given the acute onset of neuropsychiatric symptoms in the setting of recent herpes zoster infection, viral encephalitis was considered in the differential diagnosis. A lumbar puncture was recommended to further evaluate infectious etiologies; however,

the procedure was refused by the patient. A 21-channel electroencephalogram demonstrated diffuse generalized slowing of background activity consistent with an encephalopathic process. Magnetic resonance imaging of the brain showed no evidence of acute infarction, hemorrhage, mass lesion, or cerebellar T2/FLAIR hyperintensities suggestive of varicella-zoster encephalitis (Figure 1).

Review of the patient's medication history revealed that she had received valacyclovir at a dose exceeding the recommended renal-adjusted regimen for patients with end-stage renal disease, which is 500 mg three times weekly. In the absence of structural or infectious etiologies on neuroimaging and electrophysiologic studies, her neurologic symptoms were attributed to VAN.

Valacyclovir was immediately discontinued and emergency hemodialysis was initiated. Following the second session of hemodialysis, the patient demonstrated marked improvement in sensorium with resolution of agitation and significant reduction in visual hallucinations. After the third hemodialysis session, her neurologic symptoms had completely resolved and she was subsequently discharged in stable condition.

DISCUSSION

VAN is an established adverse effect, particularly among elderly patients and those with renal impairment, yet it remains a frequent diagnostic challenge due to its nonspecific and protean clinical manifestations. Although the association between excessive valacyclovir exposure and neurotoxicity is well described, VAN is often initially misdiagnosed as an acute neurologic emergency such as viral encephalitis, stroke, or metabolic encephalopathy, especially when patients present with an abrupt onset of altered sensorium and hallucinations.[2-4]

In the present case, the patient developed acute agitation, disorientation and vivid visual hallucinations shortly after initiation of valacyclovir, raising immediate concern for varicella-zoster virus encephalitis. Neuroimaging was therefore pursued to evaluate for infectious or structural etiologies. However, magnetic resonance imaging demonstrated no diffusion restriction or T2/FLAIR hyperintensities suggestive of encephalitis, and electroencephalography revealed only diffuse generalized slowing, a nonspecific finding commonly

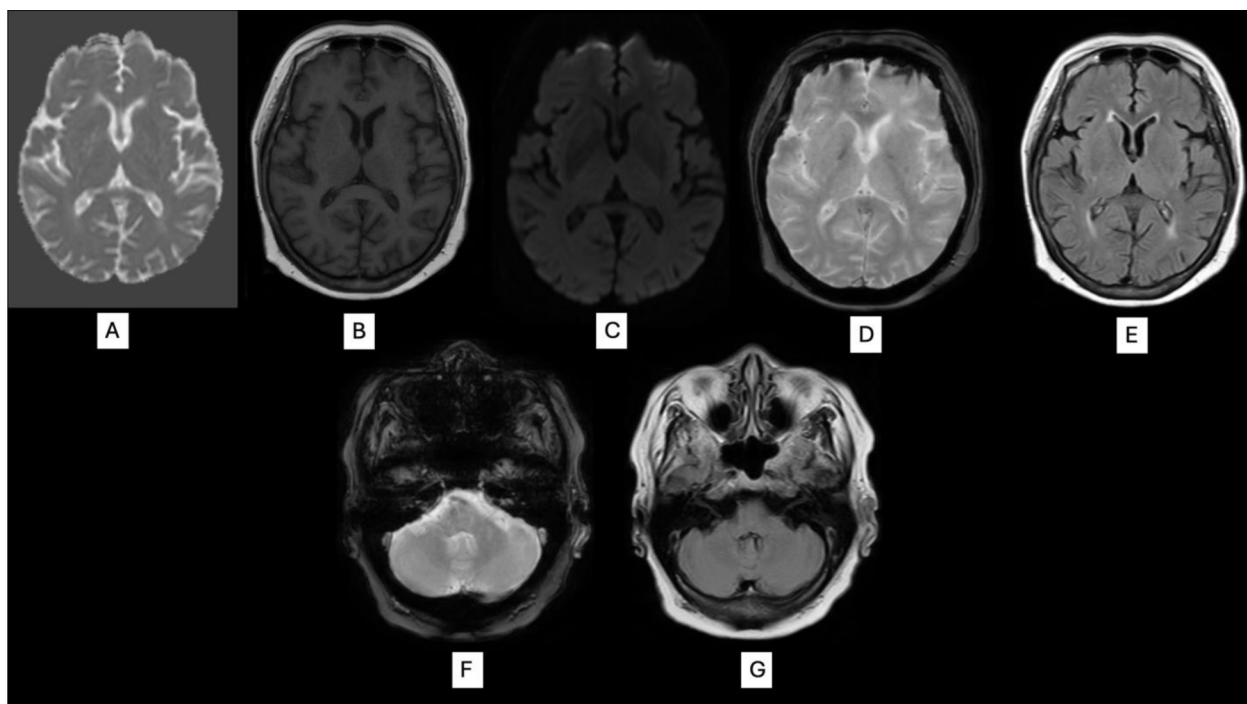


Figure 1: Plain cranial MRI (A-E: DWI, ADC, T1 and T2 sequences of the cerebrum, F-G: T2 sequences of the cerebellum showed no evidence of acute infarction, hemorrhages, mass lesions, or infection.

seen in toxic-metabolic encephalopathies.[2,5] These findings, in conjunction with the temporal relationship to valacyclovir exposure supported the diagnosis of VAN. This case presents the importance of considering medication-induced neurotoxicity early in diagnostic evaluation of acute encephalopathy, particularly in high-risk populations.

Patients with end-stage renal disease are especially susceptible to VAN due to markedly prolonged acyclovir half-life and impaired clearance of its neurotoxic metabolite, CMMG.[6,7] Accumulation of CMMG in the cerebrospinal fluid has been correlated with development of neuropsychiatric symptoms, including hallucinations and altered consciousness.[6] In this case, the patient received valacyclovir at a dose significantly exceeding the recommended renal-adjusted regimen for individuals on maintenance hemodialysis, highlighting a preventable prescribing error. Such dosing inaccuracies frequently occur in outpatient settings and remain an important source of iatrogenic morbidity in elderly patients with advanced renal disease.[3,8]

The clinical course observed in this patient further supports the diagnosis of VAN. Discontinuation of valacyclovir combined with emergent hemodialysis led to rapid and complete resolution of neurologic symptoms. Hemodialysis is effective in removing acyclovir and its metabolites with symptom improvement often noted after one to three sessions,

depending on drug burden and dialysis frequency.[1,8] Prompt recognition of VAN is therefore crucial, as timely intervention can prevent unnecessary diagnostic procedures, prolonged hospitalization and potential progression to severe complications such as seizures or coma.[2,6]

This case adds to the existing literature by emphasizing VAN as a diagnostic mimic of acute encephalopathy, rather than merely a pharmacologic adverse effect. In clinical practice, especially in resource-limited settings, extensive investigations for infectious or structural causes of encephalopathy may be pursued before medication toxicity is considered. A careful review of recent drug exposure and renal-adjusted dosing should therefore be an integral component of the initial assessment of acute neuropsychiatric symptoms in patients with renal impairment.

CONCLUSION

This case emphasizes VAN as an important and potentially reversible cause of acute encephalopathy in elderly patients with end-stage renal disease. Because its clinical presentation may closely mimic neurologic emergencies such as viral encephalitis or stroke, early recognition requires a high index of suspicion and careful review of recent medication exposure, particularly in patients receiving renally excreted antivirals. Prompt discontinuation of

valacyclovir and initiation of hemodialysis resulted in complete resolution of neurologic symptoms in this patient, showing the preventable and reversible nature of this iatrogenic complication. Increased awareness of appropriate renal dose adjustment and early consideration of medication-induced neurotoxicity may help avoid unnecessary investigations, reduce morbidity and improve clinical outcomes in high-risk populations.

ETHICAL CONSIDERATIONS

This study complies with the ethical principles set out in relevant guidelines as specified in the certificate of agreement and compliance in this research; as well as the National Ethical Guidelines for Research Involving Human Participants (NEGRHP) 2022 Edition. Paper documents (ie, consent form, printouts, case tracking sheets containing identifying information) is in a locked file cabinet when not in use. These documents are handled only by the primary investigator and corresponding co-authors. Electronic confidential data stored on transportable media such as USB, CD and portable external drive is stored securely in the said locked file cabinet as well. Documents are also password-protected and handled only by the authorized investigators and co-authors. Data will be stored for 5 years, after which the hard copies will be shredded and thrown away, and the soft copy files will be deleted.

INFORMED CONSENT PROCESS

A clearly written informed consent form was obtained, understood and signed by the patient's mother and sister, a legally acceptable representative, securing their consent for presentation, publication of the case, including other diagnostic results and images. The primary investigator, not the primary physician of the patient, obtained consent. Since the patient's mother and sister are college graduates, and they were knowledgeable and comfortable with the English language, a written informed consent form in English was used to obtain consent.

VULNERABILITY

The subject in this research was a patient of the secondary investigator of this research. Nevertheless, vulnerability was reduced with the primary investigator obtaining consent for the

patient. Since the patient is considered to be a part of the vulnerable population, informed consent was obtained from the patient's mother and older sister by the principal investigator.

PRIVACY AND CONFIDENTIALITY

The patients' confidentiality is protected by removing patient identifiers in the case report, with full compliance to the Data Privacy Act of 2012 and its implementing rules and regulations in 2016.

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None.

Authors' Contributions

Conceptualization - MJT and JBD; Data curation - MJT and JBD; Formal analysis - Not applicable; Funding acquisition - Not applicable; Investigation - MJT and JBD, Methodology - Not applicable; Project administration - Not applicable; Resources - MJT and JBD; Software - Not applicable; Supervision - MJT and JBD; Validation - MJT and JBD; Visualization - MJT and JBD; Roles/Writing - original draft - MJT and JBD; Writing - MJT and JBD. All the authors have read and approved the manuscript.

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Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declaration of Generative AI And AI-Assisted Technologies

None.

Declaration of Interests

None of the authors has any conflict of interest to disclose.

Consent for Publication

The consent for publication of collected data is secured as part of the informed consent of the participant. It was reassured to the participant that all data will be anonymized and privacy will be upheld.

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