CASE REPORT

Herpes zoster encephalopathy or acyclovir neurotoxicity: a management dilemma

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SUMMARY

This is a case report of a 69-year-old morbidly obese woman who presented with mental status changes after she was treated with acyclovir for shingles. The predominant symptoms were word-finding difficulties and visual hallucinations. Complicating her presentation was acyclovir-induced acute renal injury causing her creatinine level to rise up to 7.4 mg/dL. Acyclovir was discontinued on the suspicion of acyclovir neurotoxicity. Even though PCR for varicella zoster virus in the cerebrospinal fluid was positive, acyclovir was not restarted and the patient continued to improve and returned to her baseline.

BACKGROUND

Clinically differentiating zoster encephalopathy from acyclovir neurotoxicity is very challenging. Zoster encephalopathy should improve with acyclovir, while drug-induced neurotoxicity will get worse if the medication is continued. Clues to acyclovir neurotoxicity include visual hallucinations and dysarthria. Cerebrospinal fluid (CSF) analysis and MRI is needed to assist in the diagnosis. However sometimes, even in the presence of positive PCR for varicella zoster virus (VZV) in the CSF, acyclovir needs to be discontinued when it is suspected to be responsible for neurotoxicity especially in the presence of acute renal injury.

CASE PRESENTATION

A 69-year-old woman presented to the emergency department (ED) with nausea, dizziness and a vesicular rash on the left side of her face. Two days earlier she had been seen by her general practitioner, diagnosed with shingles and placed on oral acyclovir 800 mg five times a day. Her history was significant for uncontrolled diabetes and asthma requiring frequent courses of systemic prednisone. In the ED she was afebrile and her vital signs were stable. Clinical examination revealed a morbidly obese woman (147 kg) with grouped vesicles just lateral to her left eyebrow, extending superiorly to her scalp. There was no redness of her eyes. Laboratory studies revealed normal leucocyte count and normal creatinine. She was given one dose 1.5 g intravenous acyclovir (10 mg/kg), ketorolac 30 mg, ondansetron 4 mg and was admitted to the hospital. Later that day, after nausea subsided and she was able to tolerate oral medications, she was discharged home on oral acyclovir. The next day the patient returned to the ED reporting episodes of acute confusion and word-finding difficulties. She also reported occasional visual hallucinations

but was unable to expand on these symptoms. She denied any fever, headache, nausea, vomiting, new rash or progression of her facial rash. She was afebrile, haemodynamically stable, oriented to person, place and time without aphasia or focal neurological deficits. Occasionally she would pause and stutter while speaking, but phonation was clear without slurring and content was appropriate. Zoster rash showed signs of improvement in the form of crusting. Laboratory studies revealed leucocytosis ($13.6 \times 10^9/L$) and acute kidney injury (creatinine 3.94 mg/dL). CT of the head revealed prominent cortical sulci in the right frontal lobe, no acute ischaemia or haemorrhage. At this time the differential diagnoses entertained included herpes zoster encephalitis versus uraemic encephalitis versus acyclovir neurotoxicity. She was given intravenous fluids and acyclovir dose was reduced to 550 mg intravenous once daily. Urgent lumbar puncture for CSF cytology, PCR for herpes simplex virus (HSV), VZV and an urgent MRI were undertaken. The next day, she was evaluated by the neurologist who recommended discontinuing acyclovir as her clinical, imaging and initial laboratory findings were not consistent with viral encephalitis.

INVESTIGATIONS

CSF analysis revealed white cell count $4/\mu L$, red blood cells (RBC) $410/\mu L$, protein 25 mg/dL and glucose 43 mg/dL. Elevated RBC count was attributed to a traumatic tap. HIV test was negative. MRI was significant for slight homogeneous bilaterally symmetric increased T2/fluid-attenuated inversion recovery (FLAIR) signal in the hippocampi and parahippocampal gyri, with scattered subcortical and periventricular non-specific T2/FLAIR white matter hyperintensities likely secondary to microangiopathic changes.

DIFFERENTIAL DIAGNOSIS

Herpes zoster encephalitis versus uraemic encephalitis versus acyclovir neurotoxicity

TREATMENT

Acyclovir was discontinued and she was given intravenous fluids.

OUTCOME AND FOLLOW-UP

Nephrology consultation was obtained. It was concluded that the patient had acute renal injury secondary to acyclovir and ketorolac use. Creatinine peaked at 7.4 mg/dL before trending down. She never became oliguric. Her speech difficulties as well as visual hallucinations resolved over the

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course of 3 days. The results of PCR for virus in the CSF were available only 4 days after discontinuation of acyclovir. PCR for HSV1 and HSV2 were negative. PCR was positive for VZV DNA. It was chosen to continue withholding acyclovir in light of her acute kidney injury as well as improving neurological status.

A month later the patient remained at her baseline without any new cognitive or physical deficits, her creatinine level was 1.37.

DISCUSSION

VZE is an increasingly recognised complication following reactivation of dormant VZV. Among the viral aetiologies of encephalitis, VZV has been reported to be the causative agent in anywhere from 5% to 15% of cases,¹ and up to 29% in one series.² Current epidemiological studies suggest that herpes zoster affects more than one million people in the USA yearly and that the incidence is increasing.³ After primary infection, VZV becomes latent in ganglionic neurons. Reactivation can occur secondary to decreased cell-mediated immunity, either from immunosuppression or age. While such reactivation usually results in zoster—commonly known as shingles—complications due to VZV can occur without the classic rash or can be temporally remote from dermatological manifestation.⁴ The ability of VZV to affect the vasculature in addition to neuronal architecture results in a great diversity of pathological processes. Neurological involvement following reactivation classically includes postherpetic neuralgia and vasculopathy; however, there is increasing recognition of encephalitis, myelopathy, cerebellitis, retinal necrosis and myriad other clinical presentations of VZV reactivation.^{3–5} Treatment of VZV encephalitis is with intravenous acyclovir.^{5–6} Acute renal injury secondary to crystal nephropathy is a well-known side effect of acyclovir, but it can also cause renal injury independent of crystalluria.⁷ Neurotoxicity on the other hand is considered a less common side effect of acyclovir. This is seen often in patients with renal impairment and there are many reports of acyclovir neurotoxicity in patients on dialysis.^{8–9} Some authors have described visual hallucinations and dysphasia—as was seen in our patient—as unique features of acyclovir neurotoxicity.^{8–10} The role of testing acyclovir levels in the blood and even in CSF has been evaluated^{11–13} and has not been found to be uniformly helpful. Differentiating acyclovir neurotoxicity from zoster encephalitis can be challenging,¹⁴ and management of the two conditions is diametrically opposite. As opposed to zoster encephalitis, acyclovir neurotoxicity is associated with normal CSF findings and normal CT scan and MRI findings. Withdrawal of acyclovir often leads to resolution of neurological symptoms in 48–72 h,^{8–10–13} but some patients require haemodialysis.^{8–9–12–15} Some authors have suggested a therapeutic trial of haemodialysis to help distinguish the two conditions.^{8–9} In our patient, neurological symptoms at the time of presentation were felt to be either due to zoster encephalitis or uraemic encephalopathy. However, she had also received a very high dose of acyclovir on account of her weight and acyclovir neurotoxicity was also considered. Initially acyclovir was continued, but the dose was reduced based on her reduced creatinine clearance. Her initial CSF and MRI studies were not consistent with zoster encephalitis and with rising creatinine levels, decision was made to discontinue acyclovir. After this, her mental condition improved, in spite of increasing creatinine, suggesting that her neurological symptoms were due to acyclovir toxicity and not due to zoster encephalopathy or uraemia. Even though the PCR for VZV in the CSF came back positive a few days later, acyclovir was not reintroduced and the patient was maintained

on close neuro checks and she continues to do well 2 months after her initial presentation.

Our case highlights the difficulties involved in the care of a patient with herpes zoster who presents with mental status changes. MRI and CSF studies help in making the diagnosis of zoster encephalitis. In our patient CSF was positive for VZV by PCR. Zoster encephalitis is treated with intravenous acyclovir which carries the risk of nephrotoxicity as well as neurotoxicity both of which were seen in our patient. Our patient recovered in spite of being treated with acyclovir for only 5 days raising another unanswered question about the optimal duration of acyclovir therapy for zoster encephalitis.

Learning points

- ▶ Mental status changes in a patient with herpes zoster on acyclovir could be due to worsening infection, but could also be due to acyclovir neurotoxicity.
- ▶ Acyclovir neurotoxicity is seen more often in conjunction with renal dysfunction.
- ▶ Visual hallucinations and speech difficulties may point to a diagnosis of acyclovir neurotoxicity.
- ▶ The exact duration of therapy for zoster encephalitis is not well-defined.

Contributors All the authors have contributed to the case and have been involved with writing as well as reviewing the drafts and the final version.

Competing interests None.

Patient consent Obtained.

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