

VARICELLA ZOSTER VIRUS REACTIVATION IN HEMODIALYSIS PATIENTS: MANIFESTATIONS, TREATMENT, COMPLICATIONS AND OUTCOME

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SUMMARY – Varicella zoster virus reactivation often occurs in the setting of impaired immunity, which is generally present in patients with end-stage renal disease (ESRD). Therapy for varicella zoster virus infection is well established. However, it is often been forgotten that acyclovir dosage should be adjusted to renal function. We point to the problem encountered in clinical practice when ESRD patient presents with cutaneous herpes zoster and neurological symptoms. Clinical findings alone may prove inadequate to determine whether neurological deficit is caused by infection of the central nervous system or is a consequence of acyclovir induced neurotoxicity.

Key words: *Encephalitis, varicella zoster; Antiviral agents; Kidney failure, chronic*

Introduction

Varicella zoster virus (VZV) is an important pathogen in patients with deficient cellular immunity such as patients with end-stage renal disease (ESRD). It is known that patients with ESRD exhibit defective cellular immunity, which is more affected than humoral immunity. Immune deficiency due to uremia cannot be corrected by hemodialysis¹. Reactivation of VZV usually gives rise to dermatomal unilateral cutaneous herpes zoster. Neurological sequelae of herpes zoster reactivation are infrequent except for post-herpetic neuralgia. Epidemiological studies have identified a risk of 0.5%-1% for encephalitis or cerebral vasculitis in patients with herpes zoster^{2,3}.

Acyclovir is a widely used and generally well tolerated antiviral agent. It is used with good success for herpetic infections. Neurotoxicity associated with acyclovir use is infrequently encountered⁴. We de-

scribe three cases of hemodialysis patients with VZV reactivation referred to our center.

Patients and Methods

Data were obtained by searching medical records and protocols of hemodialysis. Age, sex, time on dialysis, primary renal disease, comorbidities and detailed clinical characteristics of VZV infection were noted (localization, dissemination, complication and outcome). Diagnosis was based on clinical grounds and serology tests.

Results

We had three patients with VZV reactivation, two female and one male, aged 61-78 years, treated with hemodialysis (Table 1). Two of them had received corticosteroids for their primary renal disease. At first, they had cutaneous manifestation of VZV reactivation, later followed by other complications.

Our female patient had a history of hypertension, coronary artery disease and ESRD due to endemic

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nephropathy. Continuous ambulatory peritoneal dialysis (CAPD) was initiated first, in 1995, and from 2003 she was treated with hemodialysis three times a week. She developed typical herpes zoster eruptions on the right side of her head and neck. Dermatologist prescribed acyclovir in a dose of 5x800 mg. Two days after starting therapy, the patient came to hemodialysis confused and disoriented. After four hours of hemodialysis, the patient had normal mental status. We suspected the signs of acyclovir neurotoxicity to be due to the full dose of acyclovir and the dose was reduced immediately. Upon acyclovir dose reduction according to her renal function, the patient had no similar symptoms and her cutaneous herpes recovered completely in two weeks.

The second case was a 61-year-old male with ANCA+, anti GBM+ extracapillary glomerulonephritis who had been on chronic hemodialysis from 2009. He received corticosteroids because of his primary renal disease and for prevention of pulmonary complications. He was admitted to Department for Infectious Diseases because of disseminated cutaneous herpes zoster and parenteral acyclovir therapy was initiated immediately. Shortly thereafter, clinical deterioration ensued as the patient developed a comatose mental state. Analysis of cerebrospinal fluid (CSF)

obtained by lumbar puncture revealed pleocytosis and the polymerase chain reaction analysis (PCR) of the CSF detected VZV. After three weeks of therapy, his clinical status improved, however, shortly thereafter followed by recurrent infections and the patient died five months later.

The third case was a 72-year-old female whose primary renal disease was amyloidosis and she was also on corticosteroid therapy. Concomitant diseases included hypothyroidism and hypertension. She presented to our dialysis unit with cutaneous herpes zoster eruptions on her left arm. Oral acyclovir 800 mg twice a day was prescribed. Four days later, she was admitted to neurological emergency unit because of global amnesia and confusion. Computed tomography (CT) scan showed a hypodense zone, diagnosed as transient ischemic attack. On the next day, during hemodialysis session, fluctuating and altered mental state was observed and the patient was referred to Department of Infectious Diseases for suspicion of CNS infection. Analysis of CSF revealed pleocytosis. Repeated CT scan revealed edema of the basal temporal lobe. After three weeks of therapy with parenteral acyclovir, full recovery followed and there were no changes on CT scan.

Table 1. Characteristics of chronic hemodialysis patients with herpes zoster infection

Characteristic	Case 1	Case 2	Case 3
Age (yrs)	78	61	72
Sex	Female	Male	Female
Dialysis type	Hemodialysis	Hemodialysis	Hemodialysis
Dialysis duration (yrs)	16	2	2
ESRD etiology	Endemic nephropathy	Extracapillary GN	Amyloidosis
Comorbidity	AH, CVD	AH	AH, hypothyroidism
First symptom(s)	Dermal rash	Dermal rash	Dermal rash
Neurological symptom(s)	Confusion	Comatose mental state, confusion	Disorientation, global amnesia
Diagnosis	Clinical	Clinical, CSF, PCR	Clinical, CSF, CT
Therapy	Acyclovir oral	Acyclovir parenteral	Acyclovir oral, then parenteral
Clinical outcome	Full recovery	Fatal	Full recovery

ESRD = end-stage renal disease; AH = arterial hypertension; CVD = cardiovascular disease; CSF = cerebrospinal fluid; PCR = polymerase chain reaction; GN = glomerulonephritis

Discussion

Very few data exist on the occurrence of neurological complications of herpes zoster among patients with ESRD or those undergoing dialysis. Varicella zoster virus encephalitis can be difficult to diagnose in immunocompromised hosts since cutaneous symptoms frequently lag behind or do not appear at all^{5,6}. In such cases, the diagnosis can easily be overlooked, as other signs and symptoms are not specific. Clinical features include headache, fever, vomiting, mental changes, seizures and focal deficits.

Uremia is associated with lymphocytopenia and impaired lymphocyte function. Both T and B cells are affected. Decreased chemotaxis results in impaired acute inflammatory response and decreased cell mediated (delayed type) hypersensitivity⁷. As a result, patients with ESRD undergoing chronic hemodialysis are considered immunocompromised hosts and have higher susceptibility to infection and complications.

Treatment of herpes zoster in patients with ESRD requires special attention. Acyclovir is an effective agent for the treatment of VZV infection but is associated with significant neurotoxicity when renal clearance is reduced. Acyclovir is mainly eliminated by the kidney. It is estimated that the bioavailability of an oral dose of acyclovir is 15% to 30%. Acyclovir half-life is greatly prolonged in patients with ESRD, from normal 3 hours in adults with normal renal function to more than 20 hours in uremic patients, predisposing this group to neurological side effects that are occasionally severe, but generally reversible⁸.

It is often difficult to distinguish between herpes zoster encephalitis and acyclovir neurotoxicity on the basis of clinical findings alone. The occurrence of acyclovir induced encephalopathy can become a confounder in the clinical presentation of herpes zoster associated encephalitis.

In our case, acyclovir was prescribed in full dose and neurological symptoms started two days after therapy administration. Improvement of neurological state after four hours of hemodialysis pointed to

drug toxicity rather than infection. In the other two cases, infection was confirmed by CSF analysis and CT scan, nevertheless, it cannot be excluded that the high serum acyclovir levels contributed to prolonged neurological impairment in our patient. Unfortunately, there is no possibility to measure serum acyclovir level, which is normally 0.2-4 µg/mL. Therefore, dose adjustments are recommended for this population. For patient undergoing hemodialysis, the recommended dose is 800 mg twice daily⁹.

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Sažetak

REAKTIVIRANJE VIRUSA HERPES ZOSTERA U BOLESNIKA LIJEČENIH HEMODIJALIZOM:
OČITOVANJE, LIJEČENJE, KOMPLIKACIJE I ISHOD

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Do reaktiviranja varicella zoster virusa dolazi u bolesnika s narušenim imunim sustavom, što je gotovo univerzalna pojava u bolesnika sa završnim stadijem kronične bubrežne bolesti. Iako je liječenje infekcije varicella zoster virusom dobro poznato, često se zaboravlja da je potrebna prilagodba doze aciklovira s obzirom na bubrežnu funkciju. Želimo naglasiti problem pojave kožnog oblika herpes zosteru u kombinaciji s neurološkim simptomima. Na osnovi kliničkog nalaza ponekad nije moguće jasno razabrati radi li se o infekciji središnjega živčanog sustava ili o neurotoksičnosti aciklovira.

Ključne riječi: *Encefalitis, varicella zoster; Antivirusni lijekovi; Bubrežno zatajenje, kronično*