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Case Report

Herpes zoster fascialis sinistra on central vertigo patient suffering seizures after acyclovir oral administration: Neurotoxicity or coincidence?

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Abstract Herpes Zoster (HZ) is a painful dermatomal rash caused by reactivation of varicella-zoster virus in neuron cells. HZ affects all ages but it is more common in older and immunocompromised patients. Acyclovir is widely use to treat Herpes Zoster. Its water-solubility helps acyclovir metabolite, 9-carboxy methoxy methylguanine (CMMG) to penetrate cerebral fluid. A 33-year-old man with chief complaint of dizziness was diagnosed with central vertigo and underwent a Brain MRI. Two days before hospitalization, erythematous lesion, followed by painful zosteriform erythematous papules and vesicles, was seen on his left face, with noted malaise and appetite loss as prodromal symptoms. No cranial nerves were affected. Tzanck test revealed multinucleated giant cells due to infection. In general, laboratory results were normal, except for increased level of potassium (3 mmol/dl). Herpes Zoster Facialis Sinistra with maxillary branch involvement was diagnosed and oral acyclovir was given to the patient. Three hours after the first dose of acyclovir, convulsion was observed. The Acyclovir was discontinued, and wound therapy for the lesions was given with favorable outcomes. Brain MRI revealed many hyperintense lesions that were suggestive for toxoplasmosis infection. Acyclovir's oral half-life is 1.5-2.5 hours. 9-CMMG, a water-soluble acyclovir metabolite, can penetrate cerebrospinal fluid, hence feasible to create a neurotoxic impact in a brain defect patient, yet the cellular mechanism remains unknown. Acyclovir must be administered with caution to patients with brain defect because it has the potential to cause neurotoxicity.

Key words
Herpes Zoster; Acyclovir; 9-CMMG; Neurotoxic.

Introduction

Herpes Zoster (HZ) is a painful dermatomal rash caused by reactivation of varicella-zoster virus in neuron cells.[1] HZ affects all ages but it is more common in older and immunocompromised patients. Annually, HZ increases. The annual incidence among young adults ranges from 1.2-3.4 per 1000 people.[2] The treatment aims to accelerate recovery and reduce morbidity. Acyclovir is widely use to treat Herpes Zoster. Its water-solubility helps acyclovir metabolite, 9- carboxy methoxy methylguanine (CMMG) to penetrate cerebral fluid.[3]

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Case report

A 33-year-old man with chief complaint of dizziness was diagnosed with central vertigo and underwent a Brain MRI. Two days before hospitalization, erythematous lesion, followed by painful zosteriform erythematous papules and

Figure 1 Group of vesicle in erythematous base in fascialis sinistra V2.

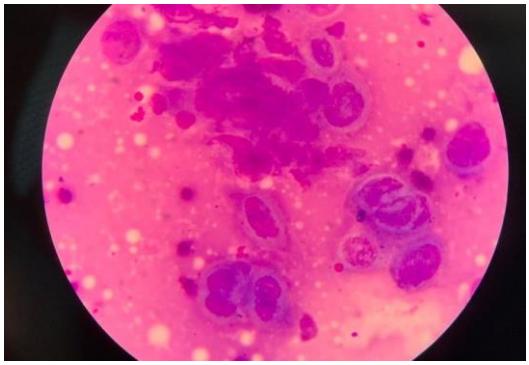

Figure 2 tzank smear: Multinucleatid giant cell.

vesicles, was seen on his left face, with noted malaise and appetite loss as prodromal symptoms, hence the patient was consulted to a dermatologist. There was no history of insect bite or application of herbal or cosmetic. The patient had never been through anything like this before. Past illnesses, such as childhood chicken pox, are documented. No history of diabetes, hypertension, or other diseases has been found. No member of the family had similar complaints. No history of drug or food allergies was found.

The general condition was good on physical examination, with compos mentis, awareness, and vital signs within normal limits. A dermatological examination of the left fascial region at n.V2 revealed grouped vesicles, erythematous papules with an erythematous macular base, erosion, and crusting **(Figure 1)**. Neurological deficits were absent. The eyes were neither hyperemic nor injected with conjunctiva.

Tzanck examination was performed by taking smear from the base of the new vesicle. On examination, we identified Multinucleated Giant Cells **(Figure 2)**, which can be used to support a Herpes Zoster diagnosis.

Routine blood tests and blood chemistry: Leukocytes 5.9 x 103/uL, Hemoglobin 12.7 gr/dl, Platelets 222 x 103/uL, Blood sugar during 140 mg/dl, Renal Function: 13 mg/dl of Urea, 0.6 mg/dl of Creatinine, Hepatic Function, SGOT: 38 U/L, SGPT 31 U/L, Electrolyte, Sodium: 139 mmol/L, Potassium: 3 mmol/L (decreased), Chloride 101 mmol/L.

The patient was diagnosed with Herpes Zoster Fascialis as high as the left n.V2 based on the history, physical examination, and supporting examinations. Acyclovir 800 mg/ 5 hours/ oral, Diclofenac Sodium 50 mg/ 12 hours / oral were administered to the patient. Treatment and cleaning of wounds with 0.9% NaCl is followed by the application of Fusidic Acid cream in the morning and evening. The patient received Vitamin B complex/ 24 hours/intravenously, dexamethasone 1 amp/ 8 hours/ intravenously, ondansetron 1 amp/ 8 hours/ intravenously, diphenhydramine 100 mg/12 hours/ intravenously, ranitidine 100 mg/12 hours/intravenously, and Pottasium suplement 1 tab/ 24 hours/ orally from the neurology department. Head MRI is planned for the patient

Three hours after receiving 800 mg of acyclovir, the patient complained seizure for a few seconds, which recurred four times until evening. It was suspected that a neurotoxic effect rather than Acyclovir administration was responsible, so the drug was discontinued and other treatments continued.

On the fourth day of control, there was no new

Figure 3 Improved clinical lesion.

vesicles, reduced redness, leaving erosional lesions with crusts **(Figure 3)**, and less pain than before VAS 3/10. The patient was administered 50 mg of diclofenac sodium orally every 12 hours for pain, as well as wound care and fusidic acid cream for morning and evening lesions. There have been no reports of seizures.

On day seven, an MRI of the head revealed multiple lesions of varying sizes in the bilateral cerebral parenchyma, midbrain, thalamus, and cerebellum. Hypointense on T1 and T2, hyperintense on FLAIR, and the presence of perifocal edema surrounding the lesion are suggestive of Brain Metastatic DD/ Toxoplasmosis **(Figure 4)**.

Discussion

Herpes Zoster increases with age in young adults, from 1.2 to 3.4 per 1000 people.[4] Most prevalent among those older than 65 years.[1,5] According to epidemiological studies, the gender ratio is nearly identical, but slightly higher for women. A Brain Metastatic DD/ Toxoplasmosis-suggestive MRI may be a risk factor for triggering Herpes Zoster. Several risk factors >50 years of age, immunosuppression, infection, psychological stress, and diabetes.

The primary goals of Herpes Zoster management are to accelerate healing, reduce pain, prevent complications, and reduce the incidence of post-herpetic neuralgia.[6] Acyclovir is an effective antiviral in the treatment of herpes simplex virus and varicella zoster virus infections. Acyclovir has an active form of triphosphate that inhibits herpes virus DNA polymerization with a potent effect while having a negligible effect on host DNA polymerization. Acyclovir triphosphate terminates the viral DNA chain prematurely. In cells infected with HSV and VZV, the virus induces a thymidine kinase that converts acyclovir to acyclovir monophosphate, the first step in drug metabolism, resulting in high levels of acyclovir in infected cells. This process may be more effective in normal cells. The half-life of acyclovir following oral administration is between 1.5 and 2.5 hours. The oral bioavailability of acyclovir is only 15-30%, and 62% of the drug is excreted through the kidneys. Therefore, patients with renal impairment can have their dosage reduced. Acyclovir is distributed throughout the body, including vesicles, cerebrospinal fluid, and vaginal secretions, and is water soluble.[1]

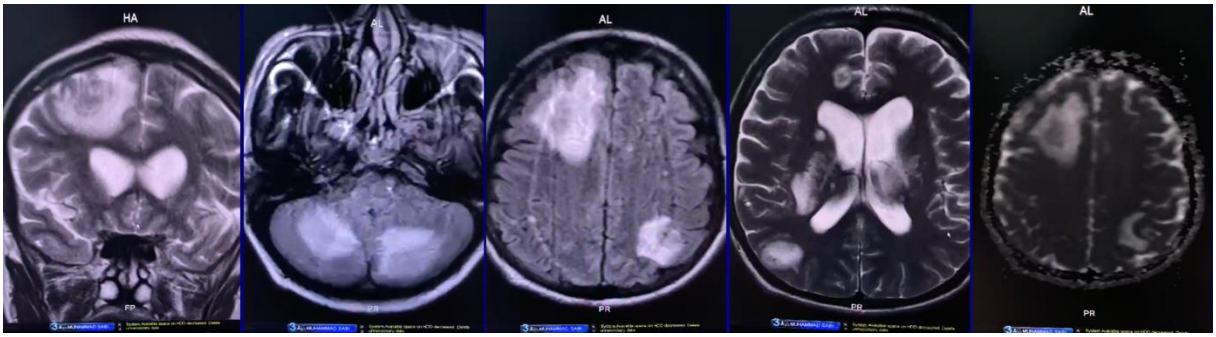

Figure 4 MRI Brain reveals multiple lesion in cerebral.

Three hours after receiving 800 mg of acyclovir, the patient complained of convulsions for a few seconds, which recurred four times until evening. It was suspected that it was a neurotoxic effect rather than giving acyclovir and then stopping the acyclovir drug and continuing other treatments. The literature indicates that acyclovir is generally well tolerated and that the incidence of side effects in patients with renal impairment is only 5%. Toxic effects on the central nervous system are uncommon, but can manifest as lethargy, tremors, and seizures. Moreover, side effects increase when used with several drugs, such as fornacet, mycophenolate, tenofovir, and zidovudine. Concurrent use of talimogene laher-parepvec, varicella vaccine, and zoster vaccine can also reduce the therapeutic effect.[1] According to other sources, the neurotoxic effect of acyclovir begins on average 3 days (0-28 days) after antiviral treatment[6]. Neurotoxic manifestations must be distinguished from the onset of viral encephalitis, which occurs approximately 7 days after the rash appears. Several case reports indicate that the neurotoxic effects of acyclovir are associated with renal impairment, as the majority of acyclovir is excreted via the kidneys. The cellular mechanism regarding the neurotoxic effect is not yet fully understood, but the water-soluble nature of acyclovir allows it to enter the cerebrospinal fluid and has the potential to have an effect on nerve cells, accompanied by an active metabolite in the form of 9-carboxymethoxymethylguanine (CMMG) that has been linked to neurotoxic events.[3] After administration of acyclovir, disorientation, decreased consciousness, hallucinations, agitation, seizures, encephalopathy, photophobia, delusions, anxiety, insomnia, and peripheral neuropathy have been reported in some cases.[6] In which the head CT scan revealed no anatomical abnormalities and the cerebrospinal fluid analysis results were within normal limits. After discontinuing acyclovir, the patient's neurological function improved without any residual symptoms.[7]

In instances where routine blood laboratory results are within normal parameters, decreased serum potassium electrolytes, kidney and liver function are also within normal parameters. Multiple lesions of varying sizes were detected in the bilateral cerebral parenchyma, midbrain, thalamus, and cerebellum. Hypointense on T1 and T2, hyperintense on FLAIR, and perifocal edema surrounding the lesion are indicative of Brain Metastatic DD/ Toxoplasmosis.

Hypokalaemic conditions exist when serum potassium levels are less than 3.5 mmol/L, with symptoms of hypokalemia appearing below 3.0 mmol/L. Frequently observed symptoms of mild hypokalemia are weakness and fatigue. If it falls below 3.0 mmol/L, the resulting symptoms may include arrhythmias. Hypokalemic conditions very rarely result in symptoms of the central nervous system, such as seizures.[8] Seizures following acyclovir administration are believed to be a side effect of acyclovir administration. Acyclovir's active metabolite, 9-carboxymethoxymethylguanine (CMMG), can enter the cerebrospinal fluid, and its vulnerability in the form of multifocal damage to the brain parenchyma has the potential to exacerbate neurotoxic symptoms.[3]

Conclusion

Acyclovir must be administered with caution to patients with brain defect because its metabolites 9-CMMG, a water-soluble acyclovir metabolite, can penetrate cerebrospinal fluid, hence feasible to create a neurotoxic, yet the cellular mechanism remains unknown.

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