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# Herpes Simplex Encephalitis: The High Cost of Collateral Damage

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## Abstract

The author discusses a case of herpes simplex encephalitis in a young man presented with headache and continuous seizures. The CNS infection with grand-mal seizures resulting in tissue breakdown and complications of acute kidney injury and lactic acidosis. Once the seizures are brought under control the lactic acidosis and the AKI resolved, but the patient tormented from the CNS squeals of HSE in the form of neuropsychiatric complications with long-term effect that necessitate 24-hour care to cope with his daily livings.

## Keywords

Herpes simplex encephalitis; Seizure; Lactic acidosis; Acute uric acid nephropathy; Redox-State; Hyperkalemia; Hyperphosphatemia; Rhabdomyolysis; Polymerase chain reaction

## Introduction

Herpes simplex encephalitis (HSE) is a devastating infection of the Central Nervous System (CNS). It is among the most commonly identified causes of acute viral encephalitis worldwide. Significant neurological damage can occur despite early initiating of therapy. Herpes simplex encephalitis is the commonest sporadic fatal viral encephalitis. The syndrome is characterized by high fever, headache, seizures, focal neurological deficits, and impaired consciousness. Type-1 Herpes simplex virus infection is the commonest cause of fatal sporadic encephalitis in the United States, accounting to 10-20% of the annual viral encephalitis. It affects all age groups and one third of cases occur in children and adolescents.

## Case history

A 32 year-old Caucasian man with no significant past medical history, admitted to the hospital with continuous seizures and changes in mental status, fever to 103F, and severe lactic acidosis (lactate level of 5.4 mmol/L, and (pH of 7.1 and bicarbonate of 10 mmol/L). His blood work up revealed hyperphosphatemia of 9.8 mg/L, high uric acid of 17.5 mg/dl. He was treated with Dilantin, lorazepam, and intravenous normal saline rehydration. His urine microscopy showed many uric acid crystals but no hematuria or proteinuria. His brain CT scan with contrast enhancement revealed hemorrhagic encephalitis involving his right frontal-temporal areas with areas of hemorrhagic necrosis. His spinal tap Cerebro-Spinal Fluid (CSF) revealed, lymphocytic pleocytosis, increased number of erythrocytes, and elevated protein. His test for herpes simplex virus DNA by polymerase chain reaction (PCR) on the CSF was positive. His electro-encephalography (EEG) was consistent with viral infection of the brain. He was treated with a course of intravenous acyclovir and continuation of the ant-seizures medications. His hospital course is complicated with acute uric acid nephropathy with high blood urea nitrogen (BUN) and creatinine. However, his kidney failure was treated symptomatically without renal replacement therapy with regaining of kidney function. His seizure was brought under control with medication, but when he was last seen in the clinic he lost most of his cognitive function necessitating 24 hours assisted care to cope with his daily function.

## Case Discussion

Herpes Simplex Encephalitis (HSE) is a devastating infection of the Central Nervous system (CNS). It is among the most commonly identified causes of acute viral encephalitis worldwide. Significant neurological damage can occur despite early initiating of therapy [1]. Intravenous acyclovir if given early is only effective in halting viral replication and prevent extensive subsequent CNS damage [2]. Behavioral and cognitive impairment are late sequelae of HSE [3]. Untreated the fatality of HSE can approach 70% with serious neurological deficits in the survival [4-8]. Impaired new learning, dysnomia, verbal and visual deficit, seizures, neuropsychiatric illness, and thromboembolic phenomena along with hyper-sexuality are but a few complications of HSE [2,3,8,9].

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Herpes simplex encephalitis is the commonest sporadic fatal viral encephalitis. The syndrome is characterized by high fever, headache, seizures, focal neurological deficits, and impaired consciousness [10]. Type-1 Herpes simplex virus infection is the commonest cause of fatal sporadic encephalitis in the United States, accounting to 10-20% of the annual viral encephalitis [4,5]. It affects all age groups and one third of cases occur in children and adolescents [1]. Herpes encephalitis caused by type-2 occurs mainly in the neonatal period, while type-1 HSV infection is the etiology of CNS diseases beyond the neonatal period [11]. The route of infection is through propagation of the viral infection via the trigeminal and olfactory nerves following an episode of HSV-1 infection of the oropharynx mainly in patients >18 year of age [4]. Reactivation of the latent virus can also occur with involvement of the CNS with predilection to the temporal lobe cortex and limbic system of the brain [12]. Toll-like receptors (TLRs) are important in the innate immunity and is expressed in the CNS where it prevent spread of the virus from the epithelium to the brain via cranial nerves through the generation of interferons. A defect in TLRs can facilitate spread of the virus to the CNS. Central nervous system infection with HSV-1 can be immune mediated [13], it is felt that both direct viral-mediated and indirect immune-mediated mechanisms play a role in producing CNS damage [4].

The diagnosis of HSE rests on the identification of the virus in the CSF using herpes simplex virus DNA by PCR. This test is highly sensitive and specific (98% and 94%) respectively [14,15]. The use of the PCR for the diagnosis of HSV-1 encephalitis has led to the identification of atypical forms of HSV-1 infection with involvement of brain stem, myelitis, or diffuse encephalitis without temporal lobe involvement [16].

Fever and seizure activity caused by the virus infection can result in lactic acidosis with serum lactate level > 4 mmol/L. Lactic acidosis occurs when the rate of lactate elimination does not match the lactate production which is usually caused by impaired tissue oxygenation. Both overproduction and reduced metabolism of lactate appear to be involved in most patients with lactic acidosis [17]. Cellular lactate production is influenced by the "redox state" of the cell with more nicotinamide adenine dinucleotide (NADH), the reduced form, over the NAD (oxidized form). NAD/NADH are involved in many cellular reactions, serving as electron acceptor or electron donor. The equilibrium between the pyruvic acid and lactic acid, which catalyzed by the enzyme lactate dehydrogenase depends on the ratio of NAD/NADH. Low NAD/NADH ratio is associated with a shift in the ratio of the pyruvate to lactate. Impairment of mitochondrial pyruvate uptake and oxidation can also result in lactic acidosis.

In humans, the major form of lactate is L-lactate, D-lactate can be a major product of gut bacteria and it is usually a minor component of mammalian metabolism. The normal production of lactic acid is 15-20mmol/Kg per day. Most is derived from glucose metabolism via the glycolytic pathway. Deamination of alanine can also generate lactate [18,19]. Lactic acid is oxidized into carbon dioxide and water in (70-80%) and to glucose in (15-20%), and a small amount is converted to alanine. These reactions occur in the liver, heart, kidneys, muscles, and other tissues. The delivery of lactic acid to the liver, where it is converted back to glucose, is called the Cori (lactic acid) cycle [18,19]. Lactate accumulation can occur as a results of the followings;

1. Increased pyruvate production
2. Reduced entry of pyruvate into the mitochondria, where it is oxidized to either carbon dioxide and water or converted to glucose
3. A shift of the cellular cytoplasmic redox state with accumulation of NADH. This drives the pyruvate/lactate ratio toward lactate.

After a grand-mal seizure or excessive exercise the lactate level could rise above 20 mmol/L [20], and the blood pH can fall as low as 6.8 [21,22]. However, the rate of lactate utilization at the same time can increase tremendously to as high as 320 mmol/hour [18] and therefore, the blood pH and plasma bicarbonate levels rapidly return to the normal range after seizure or exercise has ceased. Catecholamine surge after septic shock or acute asthmatic attack may also drive the lactate levels high and contribute to the development of lactic acidosis in patients with asthma for example [23].

Acute Uric Acid Nephropathy (UAN) is one of the 3 diseases caused by uric acid or urate crystals disposition in the kidney. Chronic urate nephropathy and uric acid nephrolithiasis are the 2 other disease which are not going to be discussed in this case [24]. The solubility of uric acid decreases dramatically when the pH is <5.5, and the solubility of urate anion increases to as high as (98%) at a physiological pH of 7.4. Acute UAN is characterized by oliguric or anuric renal failure due to precipitation of uric acid in the tubules [24,25].

Over-production and over-excretion of uric acid in patients with lymphoma, leukemia, myeloproliferative diseases, tissue catabolism and seizures can manifest as UAN. Plasma urate in these cases is usually above 15 mg/dl. The urinalysis in UAN may show uric acid crystals and the uric acid-creatinine ratio (mg/mg) is usually >1 in a random urine sample. However, the ratio is usually <0.60-0.75 in most other forms of acute kidney injury [26]. Release of other cellular constituents may also occur in marked tissue breakdown as in tumor lysis syndrome and grand mal seizure. Hyperkalemia, hyperphosphatemia, rhabdomyolysis, and hypocalcemia may result in AKI, independent of UAN [27,28]. Prevention is the best therapy for UAN via rehydration with normal saline, use of allopurinol, febuxostat, or rasburicase which converts urate into more soluble end product, allantoin.

## Conclusion

In conclusion, Herpes simplex encephalitis can cause high morbidity and mortality with complications that extends to other organs like liver, kidneys, muscles, and heart with unattended collateral damages to other vital organs, like lactic acidosis, rhabdomyolysis and pigment nephropathy as a result of tissue breakdown, and UAN with acute kidney failure. Residual neuropsychiatric sequelae following recovery of an acute episode demanded allocations of huge resources to care for these patients. The availability of limited resources may quickly be drained, and the shifting of important assets allocated for other important health problems to these patients may throw the whole health system in disarray.

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