



Herpes simplex encephalitis in a patient abusing morphine: a case report from Nepal

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Introduction: Herpes simplex encephalitis results from either primary infection with the herpes simplex virus (HSV) or reactivation of latent HSV residing within the nuclei of sensory neurons. Opioid's administration is known to reactivate HSV infection.

Case presentation: We report a 46-year-old male who was in a rehabilitation center for 17 days for abusing morphine for 2 years.

Discussion: Chronic morphine use weakens immune system thereby, making body prone for development of infection. Opioids may reactivate HSV infection because of their immunosuppressive function.

Conclusion: Herpes simplex encephalitis is a potentially fatal condition but can be treated with early diagnosis and intervention.

Keywords: encephalitis, herpes simplex, Nepal

Introduction

Herpes simplex encephalitis (HSE) is an acute or subacute illness associated with focal or global cerebral dysfunction caused by herpes simplex viruses (HSVs) belonging to either type 1 (HSV-1) or type 2 (HSV-2)^[1]. The vast majority of HSE is caused by HSV-1, with HSV-2 constituting only less than 10%^[2]. The common clinical features of HSV-1 encephalitis include altered sensorium lasting for more than 24 h and associated with other features of brain inflammation, including fever, headache, seizures, and focal neurologic deficits. Cognitive, behavioral, and personality changes have also been described^[1]. MRI is the most prominent imaging method for the diagnosis of HSE^[1]. HSE results from either primary infection with HSV or reactivation of latent HSV residing within the nuclei of sensory neurons, traditionally within trigeminal nerve ganglia^[3,4]. HSV reactivation usually occurs following trauma, steroid therapy, radiation, and stress^[4]. Administration of opioids spurs immunosuppression, thereby enabling the reactivation of HSV infection^[5]. However, more

HIGHLIGHTS

- Herpes simplex encephalitis results from either primary infection with herpes simplex virus (HSV) or reactivation of latent HSV residing within the nuclei of sensory neurons.
- Opioids may reactivate HSV infection because of their immunosuppressive function.
- Herpes simplex encephalitis is a potentially fatal condition but can be treated with early diagnosis and intervention.

extensive studies are required to explore the role of opioids in HSV. No case of HSV encephalitis due to chronic morphine use has been reported till date^[1]. Here, we report a HSE induced by chronic morphine use. This is reported in line with CARE guidelines for case reports^[6].

Case presentation

In March 2022, a 46-year-old male who was in a rehabilitation center for 17 days for abusing morphine for 2 years with no chronic medical conditions presented with a fever for 3 days, intermittent in type, the maximum recorded temperature was 101°F, not associated with chills and rigor, and not relieved by taking medications. Two days later, he developed five episodes of abnormal body movement which was acute in onset and associated with stiffness of upper and lower limbs, teeth grinding, frothing from the mouth, and tongue biting. There were no eye-rolling and no urinary or bowel incontinence. There was a total of five episodes, each lasting for 2 min and the second episode lasting about 7 min. Postictal confusion lasted for about 30 min. The patient reported no history of headache, nausea and vomiting, cough, shortness of breath, chest pain, running nose, sore throat, passage of loose stool, burning micturition, or abdominal pain. He has been smoking two packs of cigarettes a day for 10 years and consumes alcohol occasionally.

On examination, the patient was not oriented in time, place, or person, with a Glasgow Coma Scale (GCS) of 11/15 (E₃ V₃ M₅).

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On general physical examination, there was no pallor, icterus, cyanosis, clubbing, and edema. His body temperature was 101°F, blood pressure was 120/70 mmHg, heart rate was 88 beats per minute, and respiratory rate was 20 breaths per minute with 98% SpO₂ in room air. Pupils were round, regular, and reactive bilaterally. The cranial nerve examination was unremarkable. Sensory and motor were intact. His muscle bulk, tone, power, and deep tendon reflexes were normal in all four limbs. Plantar reflex was down, going on both sides. His gait, coordination, and stance were normal with no meningeal signs. Upon respiratory system examination, there is decreased air entry and basal crepitations on the right side of the chest. The cardiovascular system and gastrointestinal system were unremarkable.

The laboratory examination revealed decreased hemoglobin (11.3 g/dl), leukocyte count (7800 cells/mm³), neutrophil (70%), lymphocyte (22%), platelets (174 000 cells/mm³), increased prothrombin time (19 s) and increased international normalized ratio (INR) (1.9 s), blood urea nitrogen (16 mg/dl), creatinine (0.8 mg/dl), raised random blood sugar level (218 mg/dl), normal sodium (135 mEq/l), decreased potassium (3 mEq/l), erythrocyte sedimentation rate (30 mm/h), normal C-reactive protein (CRP) (3 mg/l), total bilirubin (0.9 mg/dl), direct bilirubin (0.3 mg/dl), increased SGOT (serum glutamic-oxaloacetic transaminase) (98 U/l) and normal SGPT (serum glutamic-pyruvic transaminase) (25 U/l). A peripheral blood smear revealed neutrophilia. Blood culture also showed no growth.

HIV Ab, HBsAg, and HCV Ab were nonreactive. Cerebrospinal fluid (CSF) fluid culture revealed no growth. The level of sugar and protein in CSF was within the normal range. Stool examination was positive for occult blood; routine urine microscopy was within normal limits. Urine toxicology was positive for tetrahydrocannabinol. MRI of the brain in T2-weighted fluid-attenuated inversion recovery (FLAIR) showed high signal intensity in the bilateral medial temporal lobe, cingulate gyri, insular region, and anteroinferior frontal lobe with parietal restriction of diffusion, which is suggestive of herpes encephalitis (Fig. 1).

The patient was clinic-radiologically diagnosed with HSV meningoencephalitis, secondary to cannabinoid and opioid dependence syndrome, and right-sided hospital-acquired pneumonia. He has managed with intravenous acyclovir 10 mg per kg 8 hourly for 4 days. He showed improvement and was discharged after a week on oral medications. Upon follow-up one-month post-discharge, he showed significant improvement.

Discussion

Encephalitis is inflammation of the brain parenchyma with neurologic dysfunction and can result from infectious, postinfectious, and noninfectious causes^[7]. Our patient had no history of intake of immune-suppressing medications or illness, travel history (both recent and remote), mosquito/tick exposure, and dog bite. Acute or chronic conditions, immunosuppressive states, and recent or remote exposure were ruled out as possible causes of encephalitis. With the help of MRI brain in T2 and FLAIR which showed high signal intensity in the bilateral medial temporal lobe, cingulate gyri, insular region, and anteroinferior frontal lobe with parietal restriction of diffusion, clinico-radiological diagnosis of herpes encephalitis was made^[8]. PCR test was not done due to unavailability at our center, which is one limitation in our case.

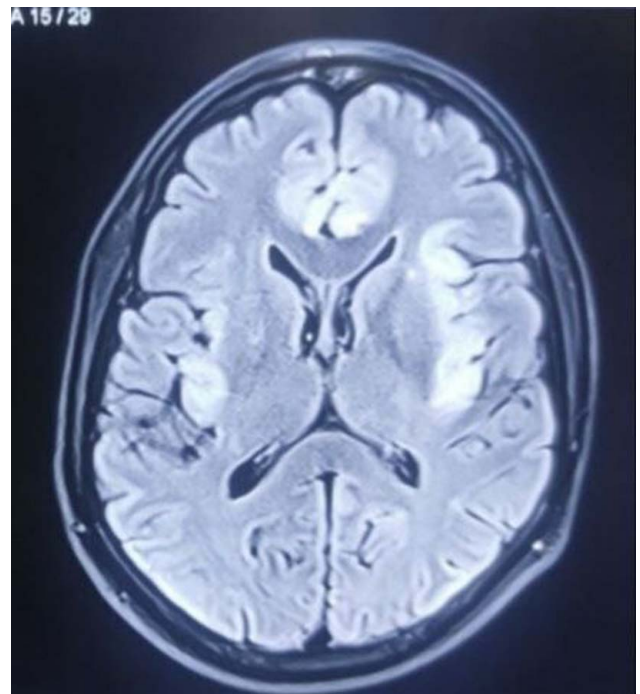


Figure 1. Magnetic Resonance Imaging (MRI) of brain in T2 weighted and FLAIR showing high signal intensity in the bilateral medial temporal lobe, cingulate gyri, insular region and antero-inferior frontal lobe with parietal restriction of diffusion.

Opioids increase the frequency of viral infections such as HSV, hepatitis C virus (HCV), respiratory syncytial virus (RSV), influenza virus, and HIV virus^[9–13]. Among them, HSV encephalitis has been an associated feature related to opioids in terms of meningoencephalitis syndromes in humans^[13]. In addition to this, radiological findings and treatment response to acyclovir favored HSV in our case. HIV and HCV were ruled out.

When someone gets infected with HSV naturally, it leads to the activation of both T and B lymphocytes, as well as specific immune reactions involving both cellular and humoral mechanisms^[14]. The ability of HSV to travel in a retrograde manner through sensory nerves from infected tissues to the sensory nerve root ganglia is what allows it to establish a lifelong infection in its host by remaining latent in that location^[15]. The immune response developed after exposure to HSV-1 is quite efficient in preventing the development of severe illness or death that could result from the infection of this virus^[16]. Opioid receptors have been identified on various immune cells, including T and B lymphocytes, dendritic cells, and other types of immune cells^[17]. Prolonged opioid treatment decreases the innate immune system by reducing the number, proliferative capacity, and recruitment of macrophages and lymphocytes. It weakens the adaptive immune system by diminishing T-cell and B-cell function, altering the expression of cytokine, and impairing T-cell apoptosis. Therefore, chronic morphine use weakens the immune system thereby making the body prone to the development of primary infection or reactivation of HSV.

Proposed pathogenic mechanisms include reactivation of latent HSV in the trigeminal ganglia with subsequent spread of

infection to the temporal and frontal lobes, primary central nervous system (CNS) infection, or perhaps reactivation of latent virus within the brain parenchyma itself^[18–22]. HSV reactivation usually occurs following trauma, steroid therapy, radiation, and stress^[5]. Therefore, the history of trauma, steroid therapy, radiation, and stress were also ruled out to identify the cause of reactivation. Our patient had a 2-year history of abusing morphine which can be the potential cause for reactivation of HSV causing HSE.

Opioids interact with viral receptors, viral proteins, and viral replication during the course of an infection^[23–25]. It is well documented that chronic opioid users have a higher prevalence of opportunistic infections, which may be directly associated with impaired immune function^[26]. Studies executed on healthy obstetric patients with no drug use disorders have revealed that opioid treatment results in the reactivation of latent viruses via dampened antiviral immune function^[27]. Similarly, Gieraerts *et al.*^[28] reported a high prevalence of HSV infection in patients receiving epidural morphine following cesarean section. In the same way, a significant association between the use of epidural morphine, which is commonly used for postoperative analgesia after cesarean section, and the reactivation of oral herpes in the obstetric population has also been reported^[29].

A study on mice showed acute morphine administration potentiates the development of encephalitis in HSV-1-infected mice^[30]. In this regard, morphine exposure decreases the integrity of the blood–brain barrier (BBB) and might explain its potential role for the involvement of BBB in the development of encephalitis in morphine-treated mice^[30]. The route by which HSV enters the CNS in humans is not fully understood and is subject to debate. The most likely pathways include retrograde transport through the olfactory or trigeminal nerves or dissemination through the bloodstream^[31]. However, the virus's preference for infecting the orbitofrontal and mesiotemporal lobes suggests that hematogenous dissemination is not the primary means of transmission. Studies conducted on animals provide evidence supporting transmission to the CNS through one or both of the trigeminal and olfactory routes. Additionally, studies suggest that viral particles can cross the anterior commissure to reach the contralateral temporal lobe^[32]. These are the evidence in favor of reactivation of herpes simplex and thus causing encephalitis. However, there have been no reports of a case of herpes encephalitis following chronic morphine use till date.

Conclusion

HSE is a fatal but fortunately treatable condition. A high index of suspicion is a prerequisite for early diagnosis and treatment. Chronic morphine use can result in herpes simplex reactivation resulting in HSE. Further studies are needed to document its true burden and pathogenesis.

Ethical approval

None.

Consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

B.K.C., H.B.B., S.S., and M.B.: wrote the original manuscript, reviewed and edited the original manuscript; M.U., A.J., S.R., S.P., C.P.L., and B.R.S.: reviewed and edited the original manuscript.

Conflicts of interest disclosure

There are no conflicts of interest.

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