Nosocomial herpes simplex encephalitis: A challenging diagnosis

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Summary Herpes simplex encephalitis (HSE) is a rare disease, but it is the most common form of sporadic encephalitis. HSE is transmitted through direct contact and developing nosocomial HSE is rarely reported in the literature. Nosocomial HSE is difficult to diagnose due to its non-specific clinical features. In this article, we present a case of nosocomial HSE that was responsible for grave consequence. We also explore its causes, outcome, and give recommendations to avoid such fatal occurrence. We stress on strict adherence to the standard precautions and preventive control measures.

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Introduction

Herpes simplex encephalitis (HSE) is the most common form of sporadic encephalitis with a global incidence of 1-4/1,000,000 population per year. The disease is challenging to diagnose and carries a bad prognosis with high morbidity and mortality rates if treatment was not given or delayed [1]. The disease can be caused by a primary herpes simplex virus type 1 (HSV-1) infection, reactivation of the latent virus in the sensory ganglia or brain parenchyma, or invasion of the central nervous system from the olfactory tract. Nosocomial HSE is extremely rare and can be responsible for grave consequences [2]. In this article, we report a case of nosocomial HSE and explore its causes.

Case report

A 55-year-old female patient, known case of multiple medical problems including diabetes,
hypertension, hypothyroidism, and chronic kidney disease with baseline serum creatinine of 150 μmol/L, presented with fever, shortness of breath, and dysuria. She is also known case of bipolar disorder on anti-psychotic medications. She was admitted through the emergency room with urosepsis, septic shock, and congestive heart failure. She was resuscitated, started on broad spectrum antibiotics, and admitted to the intensive care unit (ICU). Despite aggressive management, she developed cardiac arrest and cardiopulmonary resuscitation (CPR) was initiated followed by intubation and mechanical ventilation. She improved both clinically and biochemically (acid-base balance and renal functions) over the course of five days with extubation. Two days later she was shifted to the ward with Glasgow Coma Scale (GCS) of 15/15 and normal mental status and neurological examination. Her cardiac functions normalized and repeated full septic screen came back negative. Four weeks later, she developed a tonic–clonic seizure with decreased level of consciousness and dropping in blood pressure. She was started on norepinephrine up to 7 mcg, loaded with phenytoin and continued on maintenance dose of phenytoin. Brain magnetic resonance imaging (MRI) was normal. The patient was started empirically on meropenem, vancomycin, colistin and anidulafungin. Several electroencephalograms (EEGs) were done, which initially showed a diffuse encephalopathic process, and eventually a burst suppression pattern was observed (Fig. 1). She was also started on lacosamide and levetiracetam. Lumbar puncture was done, and the patient was started empirically on intravenous acyclovir 10 mg/kg every 8 h. Cerebrospinal fluid (CSF) analysis revealed high opening pressure, lymphocytic pleocytosis, normal glucose, highly elevated protein, and positive HSV-1 PCR. A repeat MRI revealed high signal intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) which were extensive involving temporal and frontal lobe and basal ganglia (Fig. 2). A repeat MRI showed extensive pseudolaminar necrosis with worsening of the previously observed changes of HSE (Fig. 3). Despite receiving three weeks of acyclovir treatment, unfortunately, the patient developed hospital-acquired pneumonia, septic shock and died 70 days post admission.

**Discussion**

Two distinct types of herpes simplex virus are recognized. In children and adults, the most common cause of sporadic encephalitis is herpes simplex virus type 1 (HSV-1). While in neonates, especially in the first month of life, the infection is caused by herpes simplex virus type 2 (HSV-2) [3]. Despite the fact that HSE is rare, one-third of the world population is infected with the herpes simplex virus. Primary infection typically occurs in the oropharyngeal mucosa of children and adolescents. Through retrograde axonal transport, the virus reaches the trigeminal ganglia where colonization is established. Encephalitis occurs by either extension from the olfactory tract or trigeminal ganglia into the parenchyma or through reactivation in the trigeminal ganglia with subsequent spread to the temporal and frontal lobe [1].

The onset of HSE is typically acute or subacute with a prodrome of upper respiratory or...
gastrointestinal symptoms (reported in 30–60% of the cases) [4]. Symptoms and signs of the disease are related to both the central inflammatory process caused by the virus and the infection’s predilection for the frontal and medial temporal lobes, especially the inferior portion. These include fever, headache, partial seizures, aphasia, mental and behavioral changes, and hemiparesis [5]. Diagnosis of HSE may represent a challenge especially when atypical clinical features exist. All patients presenting with fever, focal neurological deficits, seizures, or confusion warrant emergent neuroimaging and lumbar puncture. Prior to performing lumbar puncture, the treating physician should exclude contraindications such as increased intracranial pressure or uncal herniation [6].

In HSE, CSF typically reveals elevated opening pressure, lymphocytic pleocytosis, normal glucose, mildly elevated protein, and possibly elevation in red blood cells (based on severity and therapeutic intervention). CSF specimen must also be evaluated by polymerase chain reaction (PCR) for detection of viral DNA, which is considered currently the gold standard for diagnosis with a sensitivity and a specificity exceeding 95%. PCR is typically positive early in the disease course and persist for up to 4 weeks if no treatment is initiated [7]. False negative results are more likely if CSF is obtained several hours to days after initiation of acyclovir. Importantly, about 5% of CSF samples will be totally normal even though the patient has a confirmed infection by either PCR or brain biopsy [8]. Brain biopsy is currently reserved for difficult or unusual clinical presentations with typical findings including lymphocytic perivascular cuffing, glial nodules or
Figure 3 MRI of the brain showing extensive pseudolaminar necrosis with worsening of the previously observed changes of HSE. "stars", and lymphocytic infiltration accompanied by regions of necrosis [7].

MRI including diffusion-weighted imaging (DWI) can demonstrate changes of HSE as early as 40 h after the onset of symptoms. Literature suggests that 85% of HSE cases will have an abnormal MRI including hyperintense lesions in medial temporal and inferior frontal lobe on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. Contrast enhancement is common later in the disease course and may be accompanied by small hemorrhages. Involvement can be unilateral initially, but subsequent involvement of the contralateral side is a usual occurrence [9].

The EEG is abnormal in 80% of cases of HSE. Classical findings are the presence of intermittent high amplitude slow waves over the affected temporal lobes and periodic lateralized epileptiform discharges. Unfortunately, these EEG changes lack specificity, and they should be considered in the context of clinical, radiological, and CSF parameters [10].

HSE is a serious illness that requires immediate therapeutic intervention. Based upon several randomized, double-blind, placebo-controlled studies, acyclovir 10 mg/kg every 8 h for 21 days is the drug of choice. Acyclovir should also be administered in cases with strong clinical suspicion and negative results on CSF PCR due to the small, but potential risk of false negative results. Despite treatment, mortality is approximately 14–19%. Even in patients who survive following optimal medical management, long-term morbidity remains unacceptably high (45–60%) [11].

Hospital-acquired infection, also known as nosocomial infection, is an infectious process which is contracted from an environment or a health care staff facility. This can happen in various hospital environments including wards, intensive care units, operating rooms, or other clinical settings [12]. In
a large epidemiological study implemented by the World Health Organization (WHO) in 55 hospitals in 14 countries revealed an average of 8.7% of hospital patients had a hospital-acquired infection. At any time, over 1.4 million people worldwide develop an infectious complication acquired in hospitals [13]. Nosocomial infections are a major cause of morbidities and are also one of the leading causes of death. Nosocomial outbreaks are caused by poor staff compliance with standard precautions including hand hygiene, injection practices, and use of multidose vials [12]. It is well known that HSV-1 is transmitted through direct contact with herpetic lesions. Transmission of HSV-1 from person to person in the ICU is extremely rare. Several cases of HSE following neurological surgery have been reported in the literature [14]. In these circumstances, a latent period of 4–10 days is common for the onset of infection. To discover such cases early in the disease course, high index of suspicion should be practiced. In addition, neuroimaging, preferably MRI, followed by CSF analysis and HSV PCR, help to establish diagnosis in a timely manner. One study has concluded that the source of nosocomial infection of HSV-1 among newborns was in fact a medical staff who was a carrier of HSV-1 that contacted the neonates [15]. In that report, the consequences were fatal. This could be the case in our patient since we do not do screening for HSV-1 for staff (physicians, nurses, and respiratory therapists). The other possibility is reactivation of the virus, especially that the patient was immunocompromised with multiple medical problems.

**Conclusion**

We conclude that nosocomial infection with HSV-1 is dangerous and can be fatal. Lack of response to antibiotic therapy for bacterial infections in ICU patients who are treated for fever of unknown origin should raise the suspicion for alternative diagnosis including HSE. In those patients, spread of the infection from hospital personnel to patients or cross-infection among patients are possible modes of transmission. We stress on strict adherence to the standard precautions and preventive control measures. In those hospital personnel who have active HSV-1 lesions, these precautions should be more strict with prompt treatment of their lesions. We also recommend taking few days off from work until their lesions disappear.

**Conflicts of interest**

The authors declare that there are no conflicts of interest.

**References**


