Herpes Simplex Virus Meningoencephalitis Following Pulse-Dose Methylprednisolone: A Case Report and Literature Review

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Patient:	**Male, 76-year-old**
Final Diagnosis:	**Herpes simplex virus type 1 (HSV-1) encephalitis**
Symptoms:	**Encephalopathy**
Medication:	**—**
Clinical Procedure:	**Lumbar puncture**
Specialty:	**Critical Care Medicine**

Objective: Unusual or unexpected effect of treatment

Background: Several cases of herpes simplex virus type 1 meningoencephalitis (HSVE) have been reported in patients receiving steroids, but the exact contribution of steroids to the disorder remains unclear because other risk factors, such as chemotherapy, brain radiation, or surgery, were present in almost all cases.

Case Report: We report the case of a 76-year-old man who developed HSVE following the administration of pulse-dose steroids. The patient had occupational asbestos exposure and a chronic interstitial lung disease of unclear etiology (sarcoidosis versus hypersensitivity pneumonitis) and was admitted for acute-on-chronic respiratory failure requiring mechanical ventilation. After a negative infectious workup and several days of antibiotics without improvement, pulse-dose steroids were administered. In the following days, the patient developed a fever and worsening encephalopathy. A lumbar puncture showed elevated nucleated cells and positive polymerase chain reaction for herpes simplex virus 1 in the cerebrospinal fluid, confirming the diagnosis of HSVE. Acyclovir treatment was initiated, but the patient later died as a result of persistent severe encephalopathy and respiratory failure with an inability to wean mechanical ventilation.

Conclusions: Clinicians should keep in mind that HSVE is a potential complication of steroids and carefully consider the benefit/risk ratio of pulse-dose steroids, taking into account associated factors of immunosuppression. A high level of awareness should be especially maintained in critically ill patients because of associated risk factors (critical illness immune paralysis) and because neurological signs of HSVE may be missed in mechanically ventilated, sedated patients.

Keywords: Critical Care • Encephalitis, Herpes Simplex • Steroids

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Background

Herpes simplex virus (HSV) is the most common infectious cause of sporadic encephalitis worldwide, with HSV-1 being the most common strain to cause HSV encephalitis (HSVE) [1]. After primary mucocutaneous infection, HSV remains latent in sensory ganglia and 60-90% of the world's population is estimated to be seropositive for HSV [1]. Possible pathogenic mechanisms for HSVE 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, and perhaps reactivation of latent virus within the brain parenchyma itself [1]. The introduction of acyclovir has decreased mortality rates from 70% to 15% [2], but early diagnosis and treatment initiation are major determinants of mortality [2].

Immunocompromised individuals seem to be at higher risk for severe HSV infections including meningoencephalitis [3], but the precise contribution of steroids remains unclear. Owing to their anti-inflammatory and immunomodulatory effects, glucocorticoids might in theory increase the rate of viral replication, but experimental animal models have yielded conflicting results regarding their effect on replication and clearance of HSV in the CNS [4,5]. Case reports have shown temporal associations between steroids and HSVE, but the relative contribution of steroids remains unclear because other factors, such as concomitant chemotherapy [6,7] or direct insult to the CNS (radiation [8], surgery [9,10]) or close structures (eye [11,12]), may have contributed to the HSVE in most of these cases. Here, we present a case of HSV-1 meningoencephalitis that developed following pulse-dose steroids for the treatment of interstitial lung disease in a patient with no history of chemotherapy or CNS insult. This case highlights the potential risk of pulse-dose steroids in patients with associated risk factors (age, critical illness immune paralysis, lymphopenia) and the need to rule out CNS infection in case of persistent, unexplained encephalopathy in critically ill patients. Informed consent for publication was obtained from the patient's next of kin.

Case Report

A 76-year-old man was admitted with acute-on-chronic hypoxic respiratory failure. He had a past medical history of ischemic cardiomyopathy with reduced ejection fraction, atrial fibrillation, and ventricular tachycardia requiring a pacemaker and amiodarone, and he was on home oxygen owing to chronic hypoxic respiratory failure. The patient had a significant smoking history and occupational asbestos exposure. A year prior to admission he underwent the following procedures for dyspnea: (1) a pulmonary function test that showed normal spirometry, decreased lung volumes, and severely impaired diffusion

capacity, consistent with restrictive lung disease; (2) a chest computed tomography (CT) scan that revealed perilymphatic nodular opacities (some calcified), ground glass opacities, and lower lobe predominant septal thickening; and (3) unremarkable bronchoscopy and broncho-alveolar lavage. A repeat chest CT a month prior to admission revealed worsening interstitial lung disease concerning for sarcoidosis versus chronic hypersensitivity pneumonitis. On admission, the patient was afebrile with a normal neurological exam. Significant laboratory values included white blood cell count 11.4×10^9/L (lymphocytes 0.66×10^9/L), procalcitonin 0.15 ng/mL, C-reactive protein 10.3 mg/dL, and brain natriuretic peptide 5374 pg/mL. A chest CT showed no acute pulmonary embolus, but new ground glass and consolidative opacities were observed in both upper lobes. The patient was started on antibiotics for presumed community-acquired pneumonia and diuretics for heart failure exacerbation. He required intubation and mechanical ventilation on day 3 for worsening acute hypoxic respiratory failure. An extensive infectious workup, including 2 bronchoscopies with broncho-alveolar lavage, was entirely negative (bacterial and fungal cultures, multiplex polymerase chain reaction (PCR) for respiratory viral panel performed on a nasal swab and broncho-alveolar lavage fluids, *Pneumocystis jirovecii* PCR, acid fast bacillus cultures). Serum levels of immunoglobulins were normal for IgA and IgM and elevated for IgE (388 IU/mL, normal values <100 IU/mL) and IgG (1631 IU/mL, normal values 700-1600 IU/mL). An echocardiogram showed an ejection fraction of 45%, which was unchanged from prior examination. On day 5, given the lack of respiratory improvement after several days of antibiotics and diuretics, methylprednisolone at 46 mg/d was started to treat possible cryptogenic organizing pneumonia versus amiodarone-induced lung toxicity versus sarcoidosis. No improvement was subsequently observed and on day 11 steroid dosage was increased to 1000 mg/d for 3 days.

On day 13, the patient became febrile with worsening hyperleukocytosis; urine culture was positive for *Candida albicans*, blood culture for *Candida parapsilosis*, and sputum culture for methicillin-sensitive *Staphylococcus aureus*. The patient was started on caspofungin.

Within the next few days, attempts to wean sedation and mechanical ventilation were unsuccessful. The patient was intermittently following commands during sedation holidays, but he was very tachypneic with patient/ventilator dyssynchrony, requiring sedation to be maintained. On day 18, the patient was noted to be minimally responsive to commands, which was a worsening of his mental status from previous days. He was febrile again and his white blood cell count was 20.1×10^9/L. A head CT scan was unremarkable, but a brain MRI could not be obtained due to the pacemaker. A lumbar puncture was performed, and cerebrospinal fluid studies were significant

for nucleated cells of 36/µL (92% neutrophils), red blood cells of 8000/µL, glucose 73 mg/dL (normal 40-70 mg/dL), protein 46 mg/dL (normal 15-45 mg/dL), and lactate 2.8 mmol/L (normal 1.1-2.4 mmol/L). Bacterial cultures were negative, but PCR results for HSV-1 were positive.

The patient was started on acyclovir 10 mg/kg every 8 h for HSV-1 meningoencephalitis. Steroids were tapered and eventually discontinued. The patient's mental status did not improve, and severe patient/ventilator dyssynchrony persisted with an inability to wean mechanical ventilation. The patient was transitioned to comfort care and died on day 25. Of note, he had remained significantly lymphopenic during the entire Intensive Care Unit (ICU) stay (lymphocyte count consistently below 0.8×10^9/L with a nadir of 0.01×10^9/L) with a CD4 count of 66/mm^3 and a CD4/CD8 ratio of 1.84. Screening for HIV and viral hepatitis yielded negative results.

An autopsy was performed, and significant lung findings included interstitial fibrosis most compatible with silicosis, pulmonary congestion, acute bronchopneumonia in the right lower lobe, and subacute infarction with necrosis and cavitation in left upper lobe. The neuropathology did not reveal any acute process.

Discussion

This case illustrates how important and challenging the discussion of the benefit/risk ratio is prior to administering pulse-dose steroids in critically ill patients. Steroids were administered in our patient, with the dosage subsequently being increased because of the lack of improvement after treatment of presumed pneumonia and heart failure exacerbation. The steroid treatment was also used because diagnoses of sarcoidosis or hypersensitivity pneumonitis were considered based on previous medical history and chest imaging. However, the autopsy ruled out these diagnoses.

The risk of developing severe HSV infection after high-dose steroids is difficult to ascertain. In patients with systemic lupus erythematosus treated with various immunosuppressive drugs, the risk of severe HSV infection is increased [3]; steroids have been specifically associated with increased rates of opportunistic infections and herpes zoster infection in this population. The hypothesis of an increased risk of HSV infection due to steroids is therefore reasonable, but it has not been conclusively proven so far. Multiple cases of steroid-associated HSVE have been reported and are summarized in **Table 1** [6-8,10-24]. In almost all cases, the presence of other potential triggers of HSVE, such as immunosuppressive drugs or direct CNS injury (surgery, radiation, eye injury), prevents any definite conclusion regarding a specific effect of steroids.

Our patient did not have a history of chemotherapy administration or direct CNS injury, but his lymphopenia on presentation was another potential risk factor for HSVE and makes a causal link between steroids and HSVE difficult to assert.

The lymphopenia consistently present in our patient throughout his admission and very low CD4 count may have indeed increased his risk of developing HSVE. Its cause remains unclear. HIV screening was negative, and the lymphopenia was ascribed on admission to possible sarcoidosis; however, the autopsy did not confirm that diagnosis. After inoculation of HSV in experimental models, antilymphocyte serum allowed the development of viremia and fatal meningoencephalitis [25]. Lymphopenia has been associated with increased risk of infection in general in patients with systemic lupus erythematosus [26], and HSVE complicating drug-induced lymphopenia has been reported [27]. Lymphopenia was present in our patient even before steroid administration, but steroids are known to decrease circulating lymphocyte count and function, especially T cells and the CD4 subset [28], and may have further altered our patient's immune system.

Critical illness and sepsis per se are associated with lymphopenia, monocyte deactivation, and immune paralysis [29]. Lymphopenia in our patient was not secondary to sepsis because it was present prior to his admission. Pre-existing lymphopenia, critical illness-induced immune paralysis, and steroids may have synergistically led to the development of HSVE. However, despite a high prevalence of lymphopenia and immune paralysis in critically ill patients, regardless of the presence of sepsis [30], the occurrence of ICU-acquired HSV is very rare [31] and its reality has even been challenged [32]. It is therefore likely that steroids played a key role in our patient even though a causal link with HSVE cannot be proven. Another concern specific to critically ill patients is that alarming neurological signs associated with HSVE may be missed in sedated, mechanically ventilated patients, which could cause delayed diagnosis and increased mortality. From that perspective, implementing daily interruption of sedation in these patients, which has been associated with better outcomes in randomized control trials [33,34], might also allow earlier detection of alarming signs, earlier diagnosis of HSVE, and improved outcome. The presence of fever, reported in 80-90% of patients with HSVE [35], should prompt a lumbar puncture when it is unexplained and associated with persistent altered mental status during sedation interruptions in immunocompromised patients.

The fact that our patient also developed a *C. parapsilosis* fungemia after steroid administration further suggests significant immunosuppression. The patient had several risk factors for candidemia (age, mechanical ventilation, central venous catheter, broad-spectrum antibiotics) [36], and whether steroids

Table 1. Summary of reported cases of herpes simplex virus meningoencephalitis associated with steroids administration.

Author	Year	Patient age/sex	Steroid	Daily dose (Prednisone equivalent)	Duration, d	Indication for steroids	Associated risk factors	HSV-1/2	Lympho-penia	Survival
Doherty et al [13]	2001	81 y/M	Hydrocort-isone	75 mg	10	Myxedema coma	Direct CNS insult due to myxedema	N/A	N/A	No
Jacobs [8]	1999	42 y/F	Dexametha-sone	50 mg	30	Brain metastases (breast)	Whole brain radiation	N/A	N/A	N/A
Jaques et al [9]	2016	24 y/M	Dexametha-sone	50 mg	8	Brain tumor	Neurosurgery	HSV-1	N/A	Yes
		53 y/M	Dexametha-sone	60 mg	18	Brain tumor	Neurosurgery	HSV-2	N/A	Yes
Tan et al [14]	2012	74 y/F	Not specified	N/A	N/A	Polymyositis	Cyclophosphamide	N/A	N/A	N/A
Sermer et al [15]	2014	55 y/M	Dexametha-sone	80 mg	28	Brain metastases (lung)	Whole brain radiation	HSV-1	N/A	Yes
Bewersdorf et al [16]	2019	60 y/F	Prednisolone	30 mg	N/A	COPD exacerbation	IgG deficiency	HSV-1	N/A	Yes
Schiff and Rosenblum [17]	1998	35 y/F	Dexametha-sone	120 mg	21	CNS lymphoma	Radiation/ neurosurgery	N/A	Yes	No
		24 y/F	Dexametha-sone	30 mg	120	Glioblastoma	Radiation/ neurosurgery/ chemotherapy	HSV-1	Yes	No
Alimohamadi et al [6]	2004	22 y/F	Prednisolone	20 mg	N/A	Ulcerative colitis	Azathioprine	N/A	No	Yes
Ng et al [24]	2019	38 y/F	Not specified	N/A	8	Glioblastoma	Neurosurgery	HSV-1	No	No
McLaughlin et al [10]	2019	72 y/M	Dexametha-sone	110 mg	4	Meningioma	Neurosurgery	HSV-1	N/A	Yes
Osterman et al [18]	2020	48 y/F	Not specified	Pulse-dose	5	Suspected limbic encephalitis	None but CSF abnormalities present before steroid administration (HSV PCR negative)	HSV-1	N/A	No
Silvano et al [19]	2007	55 y/M	Dexametha-sone	50 mg	N/A	Prophylactic cranial irradiation	Chemotherapy/ radiation	HSV-1	Yes	No
Riel-Romero and Baumann [20]	2003	15 y/M	Dexametha-sone	50 mg	N/A	Glioma	Temozolomide/ radiation	HSV-1	N/A	N/A
Peng et al [21]	2007	61 y/M	Dexametha-sone	110 mg	14	Pituitary adenoma	Neurosurgery/ radiation	N/A	Yes	Yes
Wittles et al [12]	2011	62 y/F	Prednisolone	1 mg/kg/d	14	Panuveitis	Acute retinal necrosis	N/A	N/A	No
Kim et al [11]	2012	57 y/M	Methylpredni-solone	1250 mg	5	Retinal vasculitis	Acute retinal necrosis	HSV-1	N/A	Yes
Lizarraga et al [22]	2013	32 y/F	Dexametha-sone	110 mg	77	Glomus jugulare paraganglioma	Radiation	HSV-1	N/A	Yes

Table 1 continued. Summary of reported cases of herpes simplex virus meningoencephalitis associated with steroids administration.

Author	Year	Patient age/ sex	Steroid	Daily dose (Prednisone equivalent)	Duration, d	Indication for steroids	Associated risk factors	HSV-1/2	Lympho-penia	Survival
Saito et al [7]	2016	77 y/F	Dexametha-sone	110 mg	N/A	Prophylactic antiemetic	Chemotherapy	HSV-1	Yes	Yes
Graber et al [23]	2011	48 y/F	Dexametha-sone	40 mg	N/A	Brain metastases (lung)	Radiation/ chemotherapy	HSV-2	No	Yes
		55 y/M	Dexametha-sone	80 mg	N/A	Brain metastases (melanoma)	Radiation	HSV-1	No	No
		45 y/F	Dexametha-sone	50 mg	N/A	Thyroid cancer	Neurosurgery	HSV-2	No	No

CNS – central nervous system; COPD – chronic obstructive pulmonary disease; CSF – cerebrospinal fluid; F – Female; HSV – herpes simplex virus; IgG – immunoglobulin G; M – Male; N/A – not available; PCR – polymerase chain reaction.

may have acted as an independent risk factor remains unclear given previous conflicting results [37,38]. The patient developed candidemia and HSVE a few days apart; the coexistence of HSVE and candidiasis were already reported in 3 HSVE cases by Schiff and Rosenblum [17]. Circulating immune cells of patients with candidemia display a phenotype of immunosuppression with T-cell exhaustion [39], which may have further predisposed our patient to HSVE.

Conclusions

In summary, clinicians should keep in mind that HSVE is a potential complication of steroids and carefully consider the benefit/risk ratio of pulse-dose steroids in critically ill patients, taking into account factors associated with immunosuppression. A high level of awareness should be especially maintained for critically ill patients because of associated risk factors (critical illness immune paralysis) and because neurological signs of HSVE may be missed in mechanically ventilated, sedated patients.

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