

# HIV positive patient with HSV-2 encephalitis: case report

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## SUMMARY

Incidence of brain infections in Human Immunodeficiency Virus (HIV) positive patients is reduced after the availability of current high active antiretroviral therapy (HAART). Herpes Simplex Virus type 2 (HSV-2) is an infrequent cause of encephalitis in HIV patients despite it is frequently involved in sexual transmitted infections. Here, we report a case of HSV-2 encephalitis occurring in a patient without full suppression of HIV replication within the brain.

A 38 year-old HIV infected man was admitted to our department because of recurrent generalized seizure and fever during the previous 24 hours. Eight months before our observation the patient was switched from a protease inhibitor based regimen to a rilpivirine-based regimen without any evidence of HIV-RNA replication in the plasma.

When the patient was admitted in our hospital, he was febrile and moderately confused, no deficit of cranial nerves was reported, motility was conserved, but he was unable to walk. Laboratory examinations performed at admission demonstrated an increase of cerebrospinal fluid (CSF) protein and cells with lymphocyte prevalence, and normal CSF

glucose. HSV-2-DNA and HIV-RNA were present within CSF at admission. Nuclear Magnetic Resonance imaging of the brain revealed lesions of the medial part of both temporal lobes including hippocampus without any sign of bleeding. A 21-day course of acyclovir therapy was administered with consistent improvement of clinical findings and disappearance of HSV-2-DNA within CSF. After the episode, HAART was switched to a regimen with high CSF penetrability containing abacavir, lamivudine, darunavir and ritonavir. Twelve months after HSV-2 encephalitis neurologic evaluation was normal, but symptoms of depression were reported, HIV-RNA remained undetectable, both in the plasma and CSF and CD4+ lymphocytes were above 500/ $\mu$ L. No opportunistic infection was reported. Patients switched to regimen well tolerated such those containing rilpivirine, that have poor drug concentration within CSF could be considered at risk for opportunistic infection of the brain. Further larger investigation needs to confirm this finding.

*Keywords:* HSV1, HSV2, viral encephalitis, acyclovir, HIV.

## INTRODUCTION

Encephalitis is an inflammatory process of the brain associated with neurologic dysfunction [1]. The inflammation can be favoured by differ-

ent processes: immune disorders, cancer, toxic or metabolic encephalopathies, vascular disorders, or infectious diseases [2]. Most viral infections and some bacterial infections can result in encephalitis, but this form of brain inflammation remains a rare complication with regard to the incidence of these infections [3]. The individual risk factors for the development of a central nervous system (CNS) infection after a benign infection are unknown, but recent data are consistent

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with host-related risk factors such as impairment of immune response (either increased or reduced in the different forms) [4]. Infectious encephalitis is mainly caused by viruses with herpes simplex virus (HSV) being the most frequently involved [5-7].

The incidence of herpes simplex encephalitis (HSE) is 1 per 250 000 to 500 000 population per year [8]. The age specific incidence is bimodal, with peaks in the young and the elderly [9]. Approximately 33% of the cases occur in patients under the age of 20 years, and about 50% in those over 50 years [3]. More than 90% of the HSE cases are caused by HSV-1. A study from the UK shows that HSV-2 accounts for only 2% of cases. HSV-1 and HSV-2 report two forms of encephalitis that differ on the basis of pathological and clinical findings [9-11].

HSE, although rare, can cause devastating and debilitating disease. Despite treatment, the associated mortality rate is still high (~20%), with only 2.5% of survivors returning to normality. Permanent disability, particularly cognitive and memory impairment, is common when HSV-1 is involved [11, 12].

Patients immunocompromised, such those living with Human Immunodeficiency Virus (HIV) infection are considered at high risk for a number of opportunistic infections of the brain including fungal infections and viral encephalitis [13-19]. After the introduction of the High Active Antiretroviral Therapy (HAART), a substantial decrease in the risk of opportunistic infections and an increase in survival rate are reported [13]. In some cases, HIV-RNA can be undetectable in the plasma, but may be present in the CSF, the relationship between such HIV replication and the risk of brain opportunistic infection is currently under

investigation. Here, we report a case of HSE sustained by HSV-2 in a patient recently switched to rilpivirine containing therapy, previously treated by a regimen containing darunavir.

## ■ CASE REPORT

A 38 years old man was admitted to our observation because of recurrent generalized seizure and fever during the previous 24 hours. His medical history was unremarkable until 3 years before, when HIV infection was diagnosed. A protease inhibitor (PI) based regimen was administered after diagnosis of HIV infection and the patient experienced within 4 months from initiating HAART the complete disappearance of HIV-RNA from plasma and a correspondent increase of CD4+ lymphocyte. No opportunistic infection was reported. Eight months before our observation HAART regimen was switched to a single tablet regimen with emtricitabine/rilpivirine/tenofovir disoproxil, subsequent examination revealed again an undetectable HIV-RNA and CD4+ lymphocytes above 500/ $\mu$ L. No other significant clinical event was reported before our observation.

When the patient was admitted in our hospital, he was febrile and moderately confused, no deficit of cranial nerves was reported, motility was conserved, but he was unable to walk. Severe headache was reported and impairment of short term memory was evident as assessed by Montreal Cognitive Assessment (MOCA) test. No other sign was reported by neurologic examination. Laboratory examinations performed at admission are reported in Table 1. Slight increase of cerebrospinal fluid (CSF) protein and cells with

**Table 1 - Findings of virologic, haematologic and CSF evaluation at admission.**

	<i>At admission</i>	<i>After 4 weeks</i>
CSF cells	60 (90% lymphocytes)/ $\mu$ L	10 (100% lymphocytes)/ $\mu$ L
CSF protein	73.1 mg/dl	43 mg/dl
CSF glucose	76 mg/dl	63 mg/dl
White Blood cells	10300/ $\mu$ L	8700/ $\mu$ L
Lymphocytes CD4+	399/ $\mu$ L	429/ $\mu$ L
HIV-RNA plasma	<20 copies/ $\mu$ L	<20 copies/ $\mu$ L*
HIV-RNA CSF	185 copies/ $\mu$ L	<20 copies/ $\mu$ L*

\*HIV-RNA was evaluated 3 months after admission on both plasma and CSF.

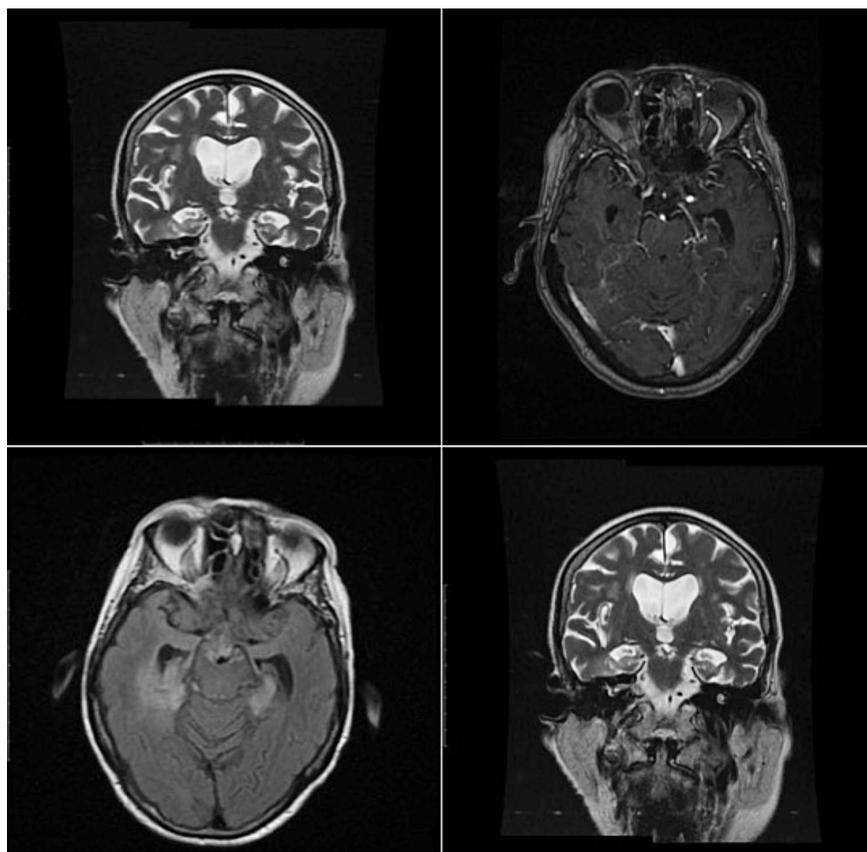
lymphocyte prevalence, and normal CSF glucose were reported. Blood and CSF cultures were negative, an extensive virologic examination on CSF specimens performed by real-time PCR showed the presence of HSV-2-DNA without any sign of other neurotropic viruses replication. HIV-RNA search by RT-PCR showed the presence of the virus within CSF, but not in the plasma. Electroencephalographic investigation revealed theta waves particularly expressed in the temporal regions. Nuclear Magnetic Resonance imaging of the brain revealed lesions of the medial part of both temporal lobes including hippocampus without any sign of bleeding (Figure 1). A 21-day course of acyclovir therapy was administered with consistent improvement of clinical findings and disappearance of HSV-2-DNA within CSF. After the HSE episode, HAART was switched to a regimen with high CSF penetrability containing abacavir, lamivudine, darunavir and ritonavir. Twelve months after HSE neurologic evaluation

was normal, but symptoms of depression were reported, HIV-RNA remained undetectable, and CD4+ lymphocytes were above 500/ $\mu$ L. No opportunistic infection was reported.

## ■ DISCUSSION

HSV-1 and HSV-2 generally produce different neurological syndromes, being herpetic encephalitis usually due to HSV-2. In immunocompetent adults HSV-2 usually causes uncomplicated genital disease, but occasional cases of neurological involvement are recognized, whose clinical manifestations range from self-limiting aseptic meningitis like illness to radiculomyelitis, and rarely encephalitis. HSV-2 encephalitis in adults is diagnosed in less than 2% of all HSV cases of encephalitis, but a growing body of evidence demonstrates that HSV-2 brain infection can result in a clinical picture suggesting encephalitis more than

**Figure 1** - Bilateral middle temporal lobe damage as assessed by FLAIR sequences without any evidence of contrast enhancement.



a meningitis and can be associated with an unfavourable outcome [20-22].

In a mouse model, HSV-2 causes higher death rates than HSV-1 through all routes of inoculation. Data deriving by murine model suggest that HSV-2 has a greater capacity to enter, transport and replicate within the CNS, as well as an enhanced ability to enter sensory nerves, followed by ganglionic transportation. These findings are not reflected in human cases, where HSV-2 does not appear to have a greater capacity to involve the CNS. As is reported in humans, HSV-2 predominantly leads to meningitis, whereas HSV-1 causes a disseminated necrotizing meningoencephalitis, in animal models [23].

Although the prognosis of herpes simplex encephalitis has been dramatically improved by the availability of specific antiviral therapy, sequelae in surviving patients may include severe neurological deficits, seizures, and neuropsychological dysfunctions that greatly impair quality of life (8). Computed tomography (CT) scanning adds little to the diagnosis other than to exclude other pathologies and to ensure that CSF sampling is safe by excluding obvious signs of raised intracranial pressure. Magnetic resonance imaging (MRI) scanning may show typical temporal lobe changes but may be normal early in disease, if diffusion weighted sequences are not performed. EEG can show a variety of abnormalities, including uni- or bilateral periodic sharp waves or attenuation of amplitude, focal or generalized slow waves or epileptiform discharges, or electrical seizures. No specific EEG patterns are pathognomonic for HSE, but a focal or lateralized EEG abnormality in the presence of encephalitis is highly suspicious of HSE. The diagnosis of HSE is generally made on the basis of typical presentation and on the presence of HSV DNA in the CSF samples. An early diagnosis is crucial in HSE as treatment is effective if started promptly, and death and disability are associated to a delayed therapy [9, 25, 26].

T-cell-mediated immunity is essential for the control of HSV; thus, immunosuppressed patients, including those undergoing organ transplant and chemotherapy, are at increased risk for severe brain opportunistic infection [27, 28]. HIV is demonstrated to penetrate early into the brain causing a subacute encephalitis and control of its replication by HAART is able to reduce electroencephalographic abnormalities [29]. Despite

HIV-infected persons are at increased risk for severe mucosal HSV reactivation, HSV encephalitis is surprisingly rare in this population, particularly after HAART was widely available in high income regions [30]. The role of HIV replication within the brain was probably crucial in the patient observed, we may speculate that a low-grade depression of cellular immunity within the brain related to low-level HIV replication favoured HSV-2 encephalitis [31]. It is notable that in several large studies of HIV-positive patients who underwent neurological evaluation, the incidence of HSV encephalitis ranged from 0% to 3%, and in the study by Cinque et al. investigating HSE in HIV only 2 cases revealed the presence of HSV-2-DNA within CSF [32].

Clinical evidence reported in our case did not differ than that observed in the general population of patients with HSE sustained by HSV-1. Seizure and fever followed by a persistent alteration of the conscience status were the presenting symptoms, as it is generally reported in the HIV negative population, and a rapid treatment permitted to avoid, at least in part, brain damage. These findings contrast with those reported in other studies investigating patients with clinical findings suggestive of encephalitis and HSV-2-DNA within the CSF suggesting that HSV-2 encephalitis is rarely associated with temporal lobe involvement and CSF pleiocytosis [33]. It is advisable that the impairment of local immunity enhanced by HIV replication favoured HSV-2 replication and subsequent brain damage.

The case suggests that patients HIV positive continue to be at risk for opportunistic infection of the brain if HIV replication is active within the brain, despite results suppressed within plasma. Routine CSF monitoring of HIV patients cannot be proposed due to the risk and low acceptability of the procedure, but other investigations, such as EEG, could be useful in highlighting indirectly the efficacy of HAART.

**No conflict of interest exists.**

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