Case report

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Herpes simplex virus simultaneous encephalitis and liver failure in an immunocompetent adult: A case report

Tiago Isidoro Duarte[1], Filipe Damião[2], Joana Ferrão[3], Tânia Sequeira[1], Filipe Sousa Cardoso[1], Nuno Germano[1]

Abstract

Herpes simplex virus (HSV) are challenging etiologic agents with a wide range of clinical manifestations. We present a case of a 34-year-old immunocompetent male who was brought to the Emergency Department (ED) with fever and prostration. In the first approach, blood tests revealed an acute hepatitis without an identified etiology. Besides the use of N-acetylcysteine, he became worse and evolved to acute liver failure and coma. HSV deoxyribonucleic acid (DNA) was identified in the cerebrospinal fluid (CSF) and blood. Although acyclovir was started on day 3, he developed cardiovascular shock with multiple organ failure and died on the 7th day of hospitalization. A high index of suspicion is needed, and early diagnosis should be promoted between clinicians.

Key words: Herpes simplex, hepatitis, acute liver failure, encephalitis.

Introduction

Herpes simplex virus (HSV) infections affect up to 80% of adults during their lifetime with a wide range of clinical manifestations. (1) The true pathogenesis in immunocompetent patients is unknown as well as why some have an indolent and mild disease and others develop multifocal infections. (2,3) To achieve that diagnosis, a high index of suspicion is necessary, because early treatment initiation plays an important role in its outcome. (1,4) Here, we describe one patient who developed both acute liver failure and encephalitis caused by HSV. Not always mental status changes are due to hepatic encephalopathy.

Case report

Thirty-four-year-old Caucasian male, with no previous medical history, was brought by a friend to the Emergency Department (ED). He presented with mental status changes and fever. He lived alone and no one knew anything from him for 3 days.

On first evaluation, he was febrile (39 ºC), prostrated, and sleepy but without other impaired neurological functions. He also presented a right conjunctival hemorrhage and abdominal generalized pain, moderate intensity, without relieving or exacerbating factors. Other vital signs were normal. Blood tests revealed leucopenia (3540 cells/ul), low platelet count (107,000 cells/ul), international normalized ratio (INR) 2.4, highly elevated C-reactive protein (CRP) (200 mg/l), elevated creatinine (1.5 mg/dl), hyponatremia (121 mmol/l), elevated lactate dehydrogenase (LDH) (3600 U/l), and increased liver enzymes (aspartate aminotransferase [AST] 1872 U/l, alanine transaminase [ALT] 954 U/l) with mild hyperbilirubinemia (2 mg/dl). Upper abdominal ultrasound (**Figures 1 and 2**) and abdominal-pelvic computerized tomography (CT) scan showed a homogenous hepatomegaly, enlarged celiac and mesenteric lymph nodes, and normal biliary structures, pancreas and spleen, with no

[1.] Department of Intensive Care Medicine, Centro Hospitalar Universitário Lisboa Central, Portugal
[2.] Department of Gastroenterology and Hepatology, Centro Hospitalar Universitário Lisboa Norte, Portugal
[3.] Department of Internal Medicine, Centro Hospitalar Universitário Lisboa Central, Portugal

Address for correspondence:
Tiago Isidoro Duarte, MD
Department of Intensive Care Medicine
Hospital Curry Cabral, Centro Hospitalar Lisboa Central
Rua da Beneficicência N8, 1050-099, Lisbon, Portugal
Tel: +351 217 924 200
Email: tiagomisidoroduarte@gmail.com

ascites. Etiological workup was negative for hepatitis A, B, C, and E, human immunodeficiency viruses (HIV) 1 and 2, cytomegalovirus, Epstein-Barr virus, and parvovirus B19. Toxoplasmosis, typhoid fever and brucellosis were also negative. Antipyretics and empiric antibiotics were initiated (ceftriaxone and doxycycline). Liver failure was considered, and N-acetylcysteine protocol was started.

Despite this, he kept prostrated but without flapping or abnormal speech. After 24 hours in the ED in surveillance, he developed an episode of generalized tonic clonic seizure, which was solved after intramuscular benzodiazepines. On post ictal period, he remained with a Glasgow coma score (GCS) <8. Brain CT scan did not show evidence of acute vascular or hemorrhagic lesions (**Figure 3**). Orotracheal intubation was performed, and he was transferred to the Intensive Care Medicine Department. Electroencephalogram (under sedation therapy) showed attenuated electric cerebral activity with no evidence of paroxysmal or focal activity. Lumbar puncture was done showing clear cerebrospinal fluid (CSF) with normal opening pressure and 1.6 cells/ul, glycorraquia of 96 mg/dl, 6 mg/dl proteins, and LDH 53 U/l.

He evolved with worsening of liver tests (INR 3, ammonia 211 umol/l, AST 11,911 U/l, ALT 3469 U/l, alkaline phosphatase 221 U/l, total bilirubin 3 mg/dl, direct 2.6 mg/dl). Repeated upper abdominal doppler ultrasound showed hepatomegaly, free fluid in the abdomen, and reduced portal blood flow (which was interpreted in the context of shock). At this point the patient met criteria for acute liver failure (ALF) and had sequential organ failure assessment (SOFA) score of 15. Noradrenaline was initiated and empiric antibacterial therapy with meningeal coverage ceftriaxone was maintained.

On the 3rd hospital day, HSV deoxyribonucleic acid (DNA) was isolated in the CSF through polymerase chain reaction (PCR). Serum blood immunoglobulin (Ig) G and IgM for HSV were also positive. Acyclovir (10 mg/kg every 8 hours) was initiated. Optic nerve sheath diameter on ultrasound evaluation was <5 mm, thus indicating low risk of intracranial hypertension. However, progressive shock with multiple organ failure persisted, with no response to organ-specific supportive care measures. Furthermore, after sedation interruption, the patient maintained a GCS of 3 with minor pupillary reflex, no corneal or deep tracheal reflexes, and bispectral monitoring of 10. Severe brain dysfunction, presumably associated with HSV infection was considered to be a contra-indication for orthotopic liver transplantation and he died on the 7th day of hospitalization.

Discussion

In immunocompetent patients, HVS hepatitis is a particularly rare condition, with few reported cases, (5,6) progression to acute liver failure in 74% and a mortality rate up to 90%. (1) Due to its rarity, there are no widely accepted guidelines for its diagnosis; thus patient history, physical examination, and blood tests with a high degree of suspicion are critical to adequate management. Our patient first clinical manifestations were fever and altered mental status with progression to seizures and coma. None of these manifestations are exclusive of HSV encephalitis or hepatitis, however some authors describe prodromal symptoms may occur. (7) Moreover, initial mental status alteration could be connected with liver encephalopathy, besides the presence of fever, which was more likely to be in favor of infection. He also did not show typical mucocutaneous lesions of herpes infection, however absence of this lesions are described in half of the patients. (6)

In the article published by Little L et al., the authors retrospectively analyzed all the HSV hepatitis-related cases within the Acute Liver Failure Study Group database, the median AST level was nearly 7800 U/l as compared to much lower levels in non-HSV hepatitis. (8) In fact, clinical sings of HSV hepatitis can include the so called “anicteric hepatitis” or “transaminitis”, characterized by normal or slightly elevated bilirubin with transaminases levels 100-1000x the upper normal limit, in association with leucopenia and thrombocytopenia.

To confirm the diagnosis of HSV hepatitis, liver biopsy can be considered. However, we did not endeavor this path, because laboratory hepatocellular pattern, serum positive serology, and CSF positive DNA HSV levels were considered enough for the diagnosis. (1,2,7,8)

Empiric treatment with acyclovir should be initiated as soon as possible. Norvell JP et al. clearly verified that early treatment with acyclovir resulted in fewer cases of ALF progressing to death or transplantation. (5) Data supports empiric treatment for all patients presenting with ALF of unknown etiology, until HSV is excluded. In disseminated disease, encephalitis is particularly feared, as it represents the most common fatal sporadic encephalitis. (9,10)

Conclusion

HSV hepatitis can be characterized by an anicteric hepatitis and diagnosed by the detection of HSV DNA levels by PCR. The evolution to disseminated forms bring a lower chance of survival. Based on the high mortality rates in untreated patients and frequently delayed diagnosis, a high index of suspicion

is needed, and early diagnosis should be promoted between clinicians.

Statement of ethics
Written informed consent was obtained from patient's parents for publication of this case report.

Disclosure statement
The authors have no conflicts of interest to declare.

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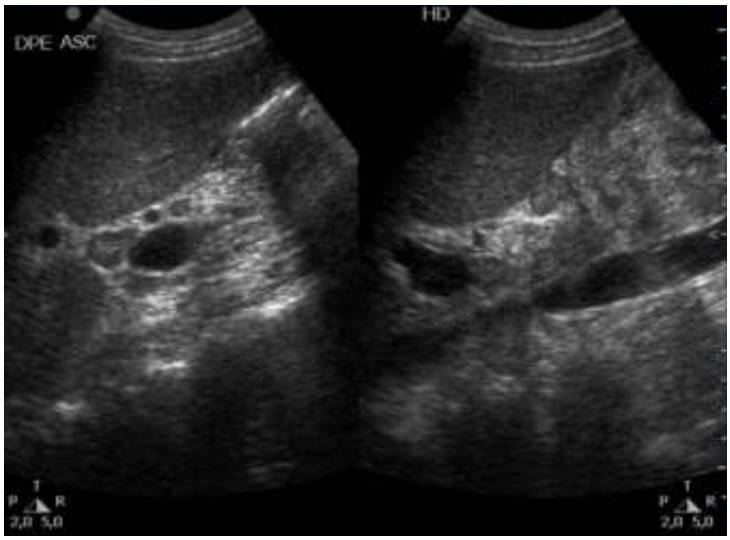
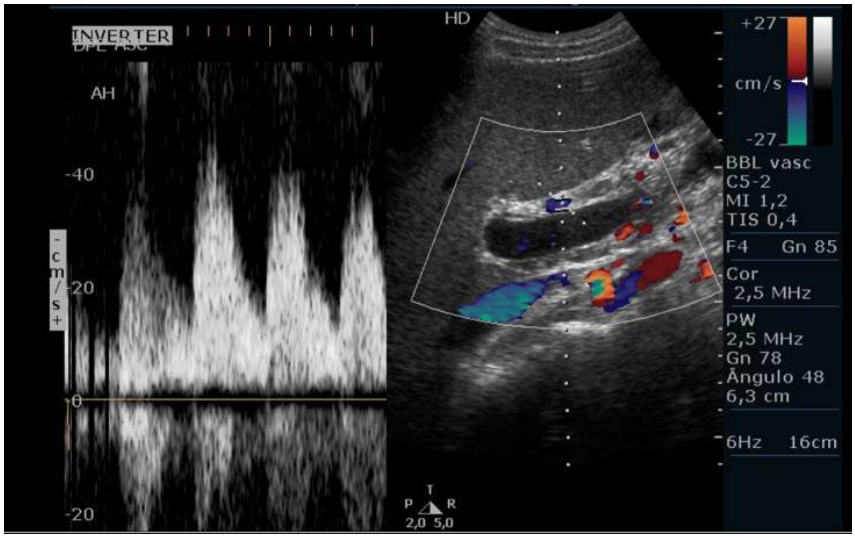
Author contributions
TID, FD, and JF performed literature review and wrote the case report. TS, FSC, and NG reviewed and corrected the paper.

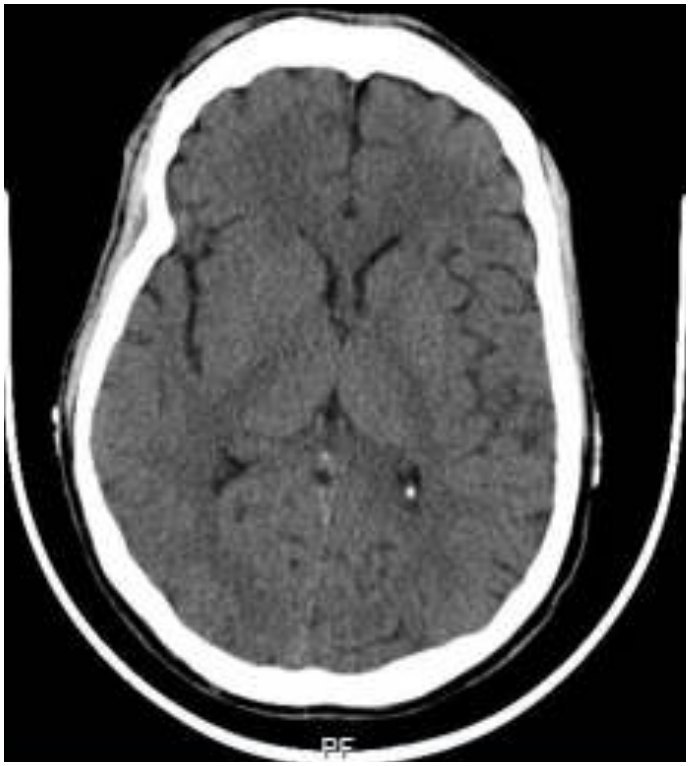
Figures 1 and 2. Upper abdominal ultrasound





Legend: Homogenous hepatomegaly with enlarged celiac and mesenteric lymph nodes, permeable arterial vessels, hepatic and portal veins on doppler evaluation.

Figure 3. Brain CT scan



Legend: CT=computerized tomography. No evidence of ischemic or hemorrhagic injuries, no space-occupying injuries.

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