Fulminant hepatitis caused by herpes virus 6 in immunocompetent adults☆

Hepatitis fulminante por herpes virus tipo 6 en adultos inmunocompetentes

Human herpesvirus 6 (HHV-6) is a lymphotropic virus of the herpesvirus family.[1] Primary infection by this virus generally affects children, causing exanthem subitum.[2,3] Liver involvement has been described more frequently in children, although cases have also been reported in young adults. While it is usually self-limiting, it can cause fulminant hepatitis requiring liver transplant.[4,5]

We report a case of acute fulminant hepatitis in our hospital caused by HHV-6 in an adult with no predisposing factors.

The patient was a 37-year-old woman with no history of interest, except for episodes of lumbosacral herpes zoster with periodic reactivations. She presented with a 10-day history of general malaise and asthenia, with no associated fever. On admission, laboratory tests showed elevated transaminases and bilirubin that gradually increased, reaching aspartate aminotransferase and alanine aminotransferase levels of 2000 U/L on the fourth day, with total bilirubin 35 mg/dL and deterioration in coagulation parameters, with maximum international normalised ratio 4.1. None of the imaging tests performed (ultrasound, chest-abdominal-pelvic computed tomography [CT]) showed chronic damage. Microbiological study was requested with serology and determination of RNA or DNA when necessary for hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis E virus, HIV, Epstein–Barr virus, cytomegalovirus, human T-lymphotropic virus-1 and parvovirus B19, ruling out acute liver damage due to these aetiologies. Iron study, copper and alpha-1antitrypsin tests were also negative. At first, the only positive test was antinuclear antibodies at a titre of 1/160, with the rest of the autoimmune study negative and normal protein electrophoresis. Given the diagnostic uncertainty and the patient's rapid deterioration, hepatic transjugular biopsy was performed, which showed >50% hepatocyte necrosis but failed to identify the cause of the liver failure. Coinciding with the analytical deterioration, the patient presented findings of severe hepatic encephalopathy, for which she was placed on the liver transplant list; transplantation was performed in less than 24 h.

Blood drawn prior to the transplant as part of the aetiological study was positive for HHV-6 using PCR in situ hybridisation, suggesting this as a possible causal diagnosis. Given the positive result of this test, herpesvirus study was requested in the liver explant, isolating HHV-6 DNA in the tissue obtained, with no other viruses detected. In blood samples obtained in the period immediately after the transplant, viral DNA was confirmed as negative.

HHV-6 is a virus of the herpesvirus family, which has been described as a cause of acute hepatitis in children and, exceptionally, in young immunocompetent adults.

Presentation is very variable. In adults, the most common form is mononucleosis syndrome.[6] Seroprevalence in adults has been shown to be around 90%.[7] It may establish as a latent infection and, therefore, can be reactivated in immunosuppressed patients with previous contact with the virus[8]; it is very difficult to differentiate it from primary infection, as the IgM in this case is not specific to acute infection. Diagnosis should be made on the basis of isolation of the virus or its antigens in peripheral blood or affected tissue by DNA in situ hybridisation techniques or immunohistochemistry.[9]

Liver involvement ranges from slightly raised transaminases to fulminant hepatitis requiring transplantation. The possibility of graft damage has also been described as a result of reactivation of the virus in patients with previous infection who become immunosuppressed following liver transplant.[7] In a Japanese study conducted in 2002, 11 patients with fulminant hepatitis of unknown aetiology were studied to rule out a viral cause; HVV-6 DNA was found in liver tissue in 7 of them (5 children and 2 adults).[10] A subsequent 2003 study assessed 15 adults with fulminant liver failure of unknown cause, finding that 12 of the 15 patients were positive for HHV-6 antigens in liver tissue; 10 of the 12 were also positive for antigens in peripheral blood.[7] No other viruses were found in the explants, and HVV-6 was only detected in 4 of 17 controls with another known cause of liver failure. With the findings of the studies conducted to date, it is very difficult to determine whether HHV-6 is the cause of the fulminant liver failure, or whether its presence is due to reactivation in this context. However, the coexistence of antigens in blood and liver tissue together with the absence of other coexisting viruses strengthens the case for this virus as the causal agent of liver failure.

In our case, the positive PCR result in both peripheral blood and the explant, the negative result immediately after the liver transplant, and the absence of other objective aetiology in the study suggests that the most likely cause for the fulminant liver failure in our patient was HHV-6.

Although considered a rare cause of acute hepatitis in adults, several cases of hepatitis have been described in the literature in which HHV-6 has been shown to be the most likely cause of this serious disease. Therefore, although diagnosis should be made with caution after excluding other known causes of liver failure, we believe that this virus should be included in the differential diagnosis of fulminant acute hepatitis in young adults.

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