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HHV-6 reactivation is often associated with CMV infection in liver transplant patients

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Abstract Human herpesvirus 6 (HHV-6) infection has been recently reported in liver transplant patients. HHV-6 is closely related to cytomegalo-virus (CMV), and some interaction between the viruses has been suggested. In this study, the post-transplant HHV-6 antigenemia was investigated in relation to symptomatic CMV infections in adult liver transplant patients. CMV infections were diagnosed by the pp65 antigenemia test and by viral cultures. HHV-6 infections were demonstrated by the HHV-6 antigenemia test and by serology. Significant symptomatic CMV infection was diagnosed in 42 of 75 patients during the first 6 months after transplantation. All CMV infections were successfully treated with ganciclovir. Concurrent HHV-6 antigenemia was detected in 21 (50%) of 42 patients with CMV infection. All HHV-6 infections were reactivations. HHV-6 also responded to the antiviral treatment, but with less clear effect. In conclusion, HHV-6 reactivation is often associated with CMV infection in liver transplant patients. The results support the suggestion that CMV and HHV-6 may have interactions.

Key words HHV-6 · CMV · Liver transplantation

Introduction

Human herpesvirus 6 (HHV-6) infection has been recently reported in liver transplant patients [1–4]. HHV-6 may cause fever and other clinical symptoms, such as neurological disorders and hepatitis [5]. We have previously demonstrated that HHV-6 may also infect the liver allograft and cause graft dysfunction [4].

HHV-6 is closely related to cytomegalovirus (CMV), with large genomic overlapping [6, 7], and some interaction between HHV-6 and CMV has also been suggested [8, 9]. It has also been reported that HHV-6 seroconversion after liver transplantation could be a marker of CMV disease [9]. In this study, we have investigated the post-transplant HHV-6 antigenemia in relation to symptomatic CMV infections in adult liver transplant patients.

Materials and methods

Seventy-five consecutive adult liver allograft recipients transplanted between 1996 and 1998 were included in the study. Basic immunosuppression consisted of combinations of steroids, azathioprine, cyclosporine or tacrolimus. Acute rejections were treated with high-dose steroids. No routine antiviral prophylaxis was given. CMV infections were diagnosed by the pp65 antigenemia test [10]

and by viral cultures. Symptomatic clinically significant CMV infections were treated with i. v. ganciclovir.

HHV-6 infections were demonstrated by the HHV-6 antigenemia test, which detects the virus-specific antigens in blood mononuclear cells. Peripheral blood samples for detection of HHV-6 antigenemia (and CMV antigenemia) were obtained weekly during the patients' hospital stay, and thereafter once a month up to 6 months after transplantation and in any case of suspected viral infection. The peripheral blood mononuclear cells (PBMC) were isolated by Ficoll-Paque density gradient centrifugation and cytocentrifuged onto microscope slides. The presence of viral antigens was demonstrated by immunoperoxidase staining and by monoclonal antibodies (MAB8533 and MAB8535, Chemicon Inc., Temecula, Calif.) against an early HHV-6-specific antigen and an HHV-6-variant B virion protein as described previously [4].

HHV-6 serology was performed in parallel. The HHV-6 antibody assay was performed by means of an indirect immunofluorescence test using HHV-6 infected HSB-2 cells (a continuous immature T-lymphoblastoid cell line) as antigens, as described in detail previously [11]. The serological diagnosis of HHV-6 infection was based on a fourfold rise in the antibody titer or increasing titers to greater than 1:160, which were also considered diagnostic [11].

Results

Clinically significant symptomatic CMV infection was diagnosed in 42 (56%) of 75 patients during the first 6 months (median 26 days, range 5–150 days) after transplantation. Only 8 of these were primary infections and 34 were reactivations. Antirejection treatment preceded CMV infection only in 8 out of 42 cases. The symptoms consisted of fever, graft dysfunction and pneumonia. CMV was also detected in 5 patients from bronchoalveolar lavage and in 15 patients from liver biopsy. All CMV infections were successfully treated with ganciclovir, and the CMV antigenemia subsided.

Concurrent HHV-6 antigenemia was detected in 21 (50%) of 42 patients with CMV infection, of which 5 of 8 were in primary CMV infections and 16 of 34 in reactivations. No crossreactivity between the CMV and HHV-6 detection methods was recorded. HHV-6 antigenemia preceded CMV antigenemia by about 7 days in 15 of 21 of cases of concurrent infection, in 5 of 5 primary infections and in 10 of 16 reactivations. The diagnosis of HHV-6 infection was confirmed by serology. All HHV-6 infections were reactivations. Symptoms of the patients, such as fever or graft dysfunction, could have partly been due HHV-6 infection, too. HHV-6 antigenemia also responded to the antiviral treatment, but the effect was less clear than with CMV.

Discussion

These results demonstrate that HHV-6 reactivation is often associated with symptomatic CMV infection. In most cases HHV-6 activation was recorded before CMV activation; in primary CMV infections HHV-6 antigenemia always preceded. It has been reported by others that HHV-6 seroconversion is a risk factor predisposing the patient to severe CMV infection [9]. Similar findings have been recorded in relation to the third beta-herpesvirus, HHV-7, which is also suggested to be a co-factor for CMV disease progression [12]. Interaction between the two beta-herpesviruses was previously recorded in the case of primary CMV infection and HHV-6 reactivation [8, 13]. The latter observation is in agreement with our results concerning primary infections, but in CMV reactivations there was also tendency that HHV-6 reactivation preceded CMV disease.

On the other hand, all herpesviruses tend to reactivate in immunosuppressed patients, and primary infections are known to be severe. The concurrent activation of CMV and HHV-6 may thus be just a consequence of the immunological situation of the transplant patients. Where the two beta-herpesvirus infections appeared at the same time, this may have been due to chance and not necessarily due to their interactions. However, HHV-6 infections are also common after liver transplantation, and the patients should not only be monitored for CMV but also for HHV-6.

In conclusion, HHV-6 reactivation was often associated with CMV infection in liver transplant patients. The results support the suggestion that CMV and HHV-6 may have interactions. In addition to CMV infection, HHV-6 should also be monitored after liver transplantation.

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References

1. Herbein G, Strasswimmer J, Altieri M, Woehl-Jaegle ML, Obert G (1996) Longitudinal study of human herpesvirus 6 infection in organ transplant recipients. Clin Infect Dis 22: 171–173

2. Schmidt CA, Wilborn F, Weiss K, Brinkmann V, Oettle H, Lohman R, Langrehr JM, Neuhaus P, Siegert W (1996) A prospective study of human herpesvirus type 6 detected by polymerase chain reaction after liver transplantation. Transplantation 61: 662–664

3. Singh N, Carrigan DR, Gayowski T, Marino IR (1997) Human herpesvirus-6 infection in liver transplant recipients. Documentation of pathogenicity. Transplantation 64: 674–678

4. Lautenschlager I, Höckerstedt K, Linnavuori K, Taskinen E (1998) Human herpesvirus-6 infection after liver transplantation. Clin Infect Dis 26: 702–707
5. Lusso P (1996) Human herpesvirus 6 (HHV-6). Antiviral Res 31: 1–21
6. Lawrence GL, Chee M, Craxton MA, Gompels UA, Honess RW, Barrell BG (1990) Human herpesvirus 6 is closely related to human cytomegalovirus. J Virol 64: 287–299
7. Efstathiou S, Lawrence G, Brown CM, Barrell BG (1992) Identification of homologues to the human cytomegalovirus US22 gene family in human herpesvirus 6. J Gen Virol 73: 1661–1671
8. Ward KN, Sheldon MJ, Gray JJ (1991) Primary and recurrent cytomegalovirus infections have different effects on human herpesvirus-6 antibodies in immunosuppressed organ graft recipients: absence of virus cross-reactivity and evidence for virus interaction. J Med Virol 34: 258–267
9. Dockrell DH, Prada J, Jones MF, Patel R, Badley AD, Harmsen WS, Ilstrup DM, Wiesner RH, Krom RAF, Smith TF, Paya CV (1997) Seroconversion to human herpesvirus 6 following liver transplantation is a marker of cytomegalovirus disease. J Infect Dis 176: 1135–1140
10. The TH, van der Bij W, van der Berg AP, van der Giessen M, Weits J, Sprenger HG, van Son WJ (1990) Cytomegalovirus antigenemia. Rev Infect Dis 12:S734–744
11. Linnavuori K, Peltola H, Hovi T (1992) Serology versus clinical signs or symptoms and main laboratory findings in the diagnosis of exanthema subitum infantum. Pediatrics 89: 103–106
12. Osman HKE, Peiris JSM, Taylor CE, Warwicker P, Jarret RF, Madeley CR (1996) Cytomegalovirus disease in renal allograft recipients: is human herpesvirus-7 a cofactor for disease progression? J Med Virol 48: 295–301
13. DesJardin JA, Gibbon L, Cho E, Supran SE, Falagas ME, Werner BG, Snydman DR (1998) Human herpesvirus 6 reactivation is associated with cytomegalovirus infection and syndromes in kidney transplant recipients at risk for primary cytomegalovirus infection. J Infect Dis 178: 1783–1786