Severe Amnesia due to HHV-6 Encephalitis after Allogenic Stem Cell Transplantation

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Dear Sir,

Immunocompromised posttransplantation patients are susceptible to a variety of opportunistic infections and reactivation of latent viral infections. In the past years, human herpesvirus 6 (HHV-6) has been recognized as an important new viral pathogen in this group of patients. We report a 46-year-old male who developed a severe short-term memory dysfunction based on a HHV-6 encephalitis after a bone marrow transplantation.

Case Report

A 46-year-old male with a 5-year history of follicular non-Hodgkin's lymphoma, 3 lines of chemotherapy including alkylating agents (2 ×) and fludarabine (1 ×), proved eligible for allogenic stem cell transplantation after having obtained a partial remission following fludarabine. However, no HLA-identical sibling donor was available, but a HLA-A, -B, -Cw, -DRB1, -DRB4, -DQB1 (12/12)-identical unrelated donor could be identified. Following myeloablative conditioning by a combination of cyclophosphamide (2 × 60 mg/kg) and total body irradiation (2 × 6 Gy), he received a T-cell-depleted bone marrow graft with 0.5×10^6 CD34+ cells/kg and 1×10^5 CD3+ T cells/kg. Posttransplantation immunosuppressive therapy consisted of cyclosporin only which was adjusted to levels between 250 and 350 ng/l. Neutrophil engraftment ($>0.5 \times 10^9$ /l) was observed after 16 days from transplantation. At that time, he also developed acute graft-versus-host disease of the skin which was treated with

prednisolone (1 mg/kg b.d.). Concurrently, a noninfectious pneumonia was diagnosed, which was treated with the combination of prednisolone and diuretics. Prophylactically, he received fluconazole, valacyclovir and co-trimoxazole. Patient and donor were both cytomegalovirus seronegative.

Seven weeks after the transplantation the patient became confused. On neurological examination a profound loss of short-term memory was noted; he was unable to retain any new information presented to him. There was also a retrograde amnesia for a few weeks and he was disorientated with regard to time and place. The neurological examination was otherwise normal including other cognitive functions such as attentiveness and concentration. Cyclosporin was discontinued and prophylactic vitamin B supplementation started. Because the possibility of a viral infection was considered, the dose of valacyclovir was raised to 3,000 mg/day. Laboratory investigation revealed no abnormalities except for a mild thrombopenia and leucopenia. Vitamin levels were normal including thiamine, and the cyclosporin level was in the therapeutic range. An MRI of the brain the next day was unremarkable. Spinal fluid analysis revealed normal protein and glucose levels, and a normal cell count. Polymerase chain reaction (PCR) on cerebrospinal fluid samples was negative for herpes simplex virus types 1 and 2, Epstein-Barr virus, varicella-zoster virus and cytomegalovirus but revealed the presence of HHV-6 DNA. IgG antibody against HHV-6 was detected while

specific IgM antibody could not be found. HHV-6 DNA was also detected in a throat swab but not in plasma. After a week the MRI of the brain was repeated and this time a slight increase in signal intensity was visible in the hippocampus and medial temporal horn on both sides (fig. 1) supporting the diagnosis of a temporal lobe encephalitis. After 3 weeks the PCR on HHV-6 in the spinal fluid had turned negative. Our patient showed a rapid and considerable improvement of symptoms. After 1 week he was still disorientated regarding time and place but he could recall 2 of 3 words presented to him. At the Mini-Mental State Examination (MMSE) he scored 27 out of 30 points. At this time he was also aware of his memory disturbance. Two weeks later the MMSE was unremarkable. However, neuropsychological examination after 2 months still identified moderate residual memory deficits.

Discussion

HHV-6 is a relatively new β -herpesvirus that was isolated for the first time in 1986 and is closely related to cytomegalovirus and especially human herpesvirus 7 [1, 2]. HHV-6 infection is endemic in humans and is commonly acquired in early childhood [1–3]. Like all herpesviruses it remains latent in the human body and can be reactivated in certain circumstances. Seroprevalence in the healthy adult population exceeds 90% [2, 3].

The most frequent manifestation of primary HHV-6 infection is exanthema sub-

Fig. 1. T₂-weighted MRI shows a slight increase in signal intensity in the hippocampus and medial temporal horn on both sides.

tum ('roseola' or 'sixth disease') in childhood, a febrile illness with a skin rash. Although the course is generally benign, central nervous system complications at times with fatal outcome have been described in previously healthy children [4]. Symptomatic HHV-6 infections in healthy adults do occur but are rare. However, in the past few years HHV-6 has been recognized increasingly as an important pathogen in the group of immunocompromised posttransplantation patients. A symptomatic HHV-6 infection in this group of patients can result from either reactivation of the latent virus in the recipient, donor transmission of HHV-6 or exogenous infection. Approximately 40–50% of stem cell transplant recipients develop HHV-6 infection [5].

HHV-6 infection after bone marrow transplantation has been associated with a range of clinical diseases including interstitial pneumonitis, fulminant hepatitis, high fever and skin rash. Also a higher incidence of idiopathic marrow suppression, severer graft-versus-host-disease and a higher incidence of Epstein-Barr virus and cytomegalovirus infections have been reported [1, 3, 6]. Besides this there is a remarkable propensity for invasion of the central nervous system. As mentioned before central nervous system complications have been docu-

mented after primary HHV-6 infections in childhood in which the virus could be isolated from the spinal fluid. Several cases of HHV-6 encephalitis have been reported in posttransplantation patients [6–12]. In one of these cases HHV-6 could be isolated from brain tissue on autopsy confirming the ability of HHV-6 to invade the central nervous system [7]. The prevalence of HHV-6 infection of the central nervous system in immunocompromised patients is not known. Like in herpes simplex virus encephalitis there seems to be a predilection for the limbic system. Severe amnesia – especially a short-term memory deficit – was part of the clinical picture in most reported patients, and MRI of the brain may show lesions in the temporal lobe and hippocampus. Besides this about half of the reported patients had seizures or epileptic activity at EEG monitoring [6–8, 12]. Also confusion, headache, tremor and insomnia are reported in several patients.

The presence of HHV-6 can be demonstrated with PCR in the spinal fluid. Besides the positive PCR on HHV-6, the spinal fluid examination was completely normal in our patient, and this has been described before [9, 10]. A normal routine cerebrospinal fluid examination as such does therefore not exclude an HHV-6 encephalitis.

Considering the treatment of HHV-6 infection, no controlled clinical trials of antiviral therapy against HHV-6 infections have been done. There have been several clinical reports that, in contrast to herpes simplex virus infections, treatment with acyclovir was less effective compared with ganciclovir and foscarnet [6–8]. However, also good recovery after treatment with acyclovir has been reported and in our patient there was a rapid improvement with just raising the dose of valacyclovir [11]. Acyclovir also showed some usefulness in the prophylaxis of HHV-6 reactivation in bone marrow graft recipients. Until now there has been not enough experience with this disease to assess the optimal treatment.

The outcome after an HHV-6 encephalitis ranges from complete recovery to death [6–12].

Conclusion

HHV-6 is an important new pathogen in the group of immunocompromised posttransplantation patients with affinity for the central nervous system. It should be considered in patients who develop new neurological symptoms after transplantation, especially amnesia.

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