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HHV6 Encephalitis in Children After Hematopoietic Stem Cell Transplantation

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Introduction

HHV-6 is a roseolovirus, existing in two distinct genetic subsets, HHV-6a and HHV-6b. Most infections are due to HHV6b. The primary infection normally happens during the first 3 years of life and the virus develops lifelong latency [1,2]. Typical symptoms as exanthema, fever, lymphadenopathy and cough resolve within a week. Secondary infections as e.g. bronchopneumia are rare in immune-competent patients [**1**].

In case of immune-suppression or immune-incompetence HHV-6B may reactivate, which is the case, especially after allogeneic hematopoietic stem cell transplantation (HSCT). 30% to 50% of the transplanted patients are reported to reactivate with HHV6-viremia, which is associated with pneumonitis, acute GvHD, bone marrow suppression, CMV reactivation and encephalitis [2,3].

HHV6-encephalitis is a severe complication with a substantial morbidity rate [4,5].

Here, we describe two different cases of HHV6 encephalitis in children who underwent HSCT in Tuebingen, Germany.

Patient 1

An eleven-year-old girl with pre-B-ALL first diagnosed three years earlier, Townes-Brocks-Syndrome and a cerebral sinus vein thrombosis three years earlier. She underwent allogeneic HSCT and was admitted to the hospital six months after transplantation with a generalized seizure with hyponatremia suspicious for SiADH-Syndrome.

The cerebrospinal fluid was found positive for HHV-6. Treatment was started with Foscavir, Cidofovir and Ribavirin. Due to an impaired liver function the medication had to be paused intermittently.

At the same time the girl developed severe intestinal graft-versus-host disease and received immune-suppressive therapy with Cyclosporine A (CSA), Dexamethasone and anti-Lymphoglobuline® (anti-Thymocyte Serum). With persistent leuko-/lymphopenia she developed a systemic adenovirus, HHV-6 infection and BK virus infection with a hemorrhagic cystitis.

Four weeks after admission she became neurologically altered for a second time with increasing confusion, loss of short-term memory, hypothermia and hypertension. MR-imaging (MRI) revealed changes fitting a CSA related encephalopathy. The EEG was significantly impaired compared to 4 weeks earlier.

Six weeks after admission the patient died due to multi organ failure with a predominant global respiratory failure.

Patient 2

A seven-year-old boy with Neuroblastoma stage 4 first diagnosed three and a half years before. Three years after diagnosis he relapsed with tumor progression in the thoracic spine and seventh rib. He was treated with local radiotherapy, received chemotherapy and was given haploidentical HSCT from his father. For remission maintenance, he was admitted for therapy with a chimerical GD2-antibody. After the first course of the antibody, the patient began to become agitated and aggressive. He then was found with an insufficient breathing effort (CO_2 80% to 90%), episodes of hypothermia and ceaseless itching. Moreover, he showed an exanthema of the upper and lower limbs.

Cerebrospinal fluid, leucocytes and plasma were found positive for HHV-6 nine weeks after HSCT. However, MRI showed no specific alterations of herpes infection except previously known PRES-typical lesions. The EEG revealed a conspicuous general pattern with continuous beta-activity and several sharp-waves. Antiviral therapy was started immediately with Ganciclovir for 14 days and Foscavir for more than three weeks.

About two to three weeks later the HHV-6 symptoms improved, the patient developed a breathing effort of its own, the exanthema decreased and HHV-6 virus was only found in leukocytes. Now, the MRI control revealed an involvement of both hippocampal regions resembling limbic encephalitis (Figure 1).

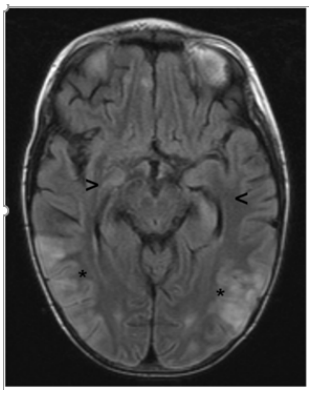

Figure 1: MRI patient 2 four weeks after diagnosis. Both hippocampal regions show alterations resembling posttransplant acute limbic encephalitis (PALE) (arrows).

Due to the immune-suppressive effect of the virus itself on the one hand and side-effects of the antiviral drugs on the other hand, he stayed persistently aplastic and lymphopenic and developed secondary

bacterial (pneumonia) and viral (systemic adenovirus und BK-virus) super-infections. He had to be re-intubated and ventilated. The patient developed severe acute respiratory distress syndrome with a consecutive pulmonary fibrotic conversion and bronchiolitis obliterans organizing pneumonia (BOOP) and additional ADV positivity. Despite veno-venous extracorporal membrane oxygenation (ECMO) to preserve the lung from additional ventilation damage the pulmonary structure did not recover, but the control CT-scan showed irreversible rapidly progressive fibrotic alterations after two weeks of ECMO. The patient died after six weeks of admission primarily due to respiratory failure.

Discussion

Until the third year of life almost every child acquires HHV-6 infection and the virus develops lifelong latency [1,2]. Consequently, nearly every immune-suppressed child is a HHV-6 carrier, positive in Leukocytes. During the course of HSCT 30% to 50% of the patients reactivate [3,6].

We describe two cases of HHV-6 encephalitis that occurred over the last 12 years at our tertiary reference center. The incidences to be found in literature vary among the different studies, here - with an incidence of 2/540 or 0.3%-HHV-6 encephalitis might be described as a rare but severe complication after HSCT.

HHV-6 encephalitis is described to occur between two and eight weeks after transplant [4]. In contrast to patient 2, who became symptomatic nine weeks after HSCT, patient 1 shows an unusually late onset. HHV-6 encephalitis is also known as PALE (post-transplantation acute limbic encephalitis) [4,7] and besides seizures, anterograde amnesia, hypothermia, and symptoms also typical of a primary infection, its onset is often accompanied by a severe hyponatremia [8]. Both patients show a different subset of symptoms but all are typical of HHV-6 encephalitis.

During the course of the disease both cases show the same problem: Both patients are heavily pretreated and immune-compromised due to underlying malignancies (B-ALL and Neuroblastoma) and received HSCT, so first the virus itself maintains leucopenia and later on the anti-viral treatment leads to persistent aplasia with bacterial (and/or viral) super-infections and secondary-in the end life-limiting-complications (liver or renal failure, respiratory failure). Therefore, it is difficult to determine the outcome of HHV-6 encephalitis itself [9].

Routine HHV-6 prophylaxis is discussed; but e.g. Betts et al. did not find an advantage in survival after HSCT for Foscavir or Ganciclovir treated non-treated patients. Nevertheless, they highly recommend frequent testing for HHV-6 (e.g. weekly testing for 4-10 weeks' post-transplant) [10]. Regarding treatment of HHV6 encephalitis, some case reports indicate that ganciclovir or foscavir may be useful. Unfortunately larger trials are still missing [11,12].

In a recent study at our center HHV-6 was found in 10 of 31 (29%) bronchoalveolar lavages performed on immune-suppressed children after HSCT at our center in Tuebingen from 2000 to 2008 (Unpublished data), HHV-6 was found in 10 samples. It was the most frequent infectious agent and did not show a certain time-pattern of appearance after HSCT. The significance concerning prophylaxis and supervision after HSCT has to be further evaluated.

In conclusion HHV-6 encephalitis after HSCT is a rare but severe complication. Even if initial treatment may be effective on HHV-6 infection and encephalitis the suppressive effect of the virus itself and the antiviral treatment may be fatal. The role of HHV-6 reactivation in children after HSCT needs further evaluation.

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