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Case Report

Clinical Relevance of High HHV-6B Viral Load in Immunocompromised Host

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Abstract

The peculiarity of the chromosomally integrated form of human herpesvirus type 6 (ciHHV-6) is its wide distribution (up to 1% of the population), the possibility of transmission by inheritance, the problem of diagnosis, including issues of differential diagnosis with the acute form of HHV-6 infection, which, in turn, makes it difficult to resolve the problem of the therapy necessity. In addition, activation of ciHHV-6 is possible sometimes with acute infection clinical symptoms and the need for antiviral therapy, especially in patients after bone marrow transplantation and chemotherapy. We report a 10-years-old girl after chiasmal-sellar germinoma surgery and subsequent chemotherapy with ciHHV-6B. The child was treated with ganciclovir. This did not significantly influence the reduction of the viral load HHV-6B DNA in serum and cerebrospinal fluid. No adverse effects of antiviral treatment were registered. It's important to exclude ciHHV-6 before the diagnosis of HHV-6 active disease is made, as this screening may prevent the unnecessary use of antivirals.

Keywords: Antiviral Therapy; ciHHV-6; HHV-6; Infection

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Introduction

Human herpesvirus 6 (HHV-6) includes 2 separate viruses, HHV-6A and HHV-6B, which differ in genetic, biological, epidemiological characteristics, pathogenic properties and clinical manifestations (1). HHV-6B causes almost all primary infections in infants and is the predominant virus associated with reactivated infection in immunocompetent and immunocompromised individuals. HHV-6A has not been associated clearly with a distinct disease and has greater neurotropism and neurovirulence (2).

The HHV-6A and HHV-6B envelope glycoprotein complex binds respectively to human CD46 and CD134 expressed on almost all cell types, especially on monocytes-macrophages (2). Saliva is assumed to be the main vehicle for virus transmission, as supported by the frequent detection

of HHV-6 in saliva and salivary glands (3, 4). Like other human herpesviruses, HHV-6 persists indefinitely in its host and is capable of reactivation, meaning the active production of detectable mature virions in some body compartments following a phase of apparently complete clearance (2). HHV-6A and HHV-6B can integrate their genomes into host chromosomes as one way to establish latency. Viral integration takes place near the subtelomeric / telomeric junction of chromosomes (5). This phenomenon has been described in 0.2% to 1% of the general population (6). Chromosomally integrated HHV-6 (ciHHV-6) positive individuals carry one integrated HHV-6 copy per somatic cell. When HHV-6 integration occurs in gametes, the virus can be genetically transmitted to offspring (inherited chromosomally integrated HHV-6, iciHHV-6) (7-9). Ci / iciHHV-6 DNA can be transmitted to recipients through blood transfusion or organ / cell donation (10).

Case Presentation

The girl K. was monitored by an endocrinologist from the age of 7 years old due to diabetes insipidus, multiple acquired pituitary insufficiency, secondary hypothyroidism, and secondary hypocorticism. At the age of 8, the child began to complain of frequent headaches. The pain was intermittent. Cranial magnetic resonance imaging (MRI) revealed no pathology.

Two years later the 10-years-old girl presented with headaches in the temporal region and visual impairment. Repeated MRI brain scan revealed an intrasuprasellar macroadenoma of the hypophysis with cystic remodeling. Within a month of hormonal therapy, the general health of the girl deteriorated. Transnasal endoscopic tumor resection performed using neuronavigation with further plasty of the Turkish saddle with a nasoseptal flap. Pathohistology of tumor material confirmed germinoma of chiasmatic-sellar region; tumor cells were loose-lying, rounded, monomorph, with eosinophilic or clear cytoplasm, prominent nucleoli, frequent mitoses; focal hemorrhages and moderate lymphocytic infiltration were seen. ICH: D2-40 (+++), Oct4 (+++). Postoperative MRI of the brain and spinal cord revealed residual tumor and postoperative changes, i.e., the formation of 20x14x15 mm with contrast enhancement in the sellar region. No abnormalities were found in the spinal cord. Chemotherapy was started.

During chemotherapy periodically subfebrile / febrile temperature, headaches in the frontal region and increased diuresis observed. The cerebrospinal fluid (CSF) examination was unremarkable. Cytological and bacteriological examination of blood and CSF was negative. Quantitative polymerase chain reaction (PCR) detected only HHV-6B DNA in CSF (3.11 log10 copies / ml) and in serum (2.7 log10 copies / ml). A revision of MRI detected no specific changes in the structure of the brain characteristic of encephalitis caused by HHV-6. Due to high HHV-6B DNA load in the CSF, ganciclovir, 5 mg / kg, was prescribed twice daily intravenously for 3 weeks, under the viral load monitoring. On the background of antiviral therapy there was a decrease in the clearance level of endogenous creatinine to 50 ml / min and ganciclovir to 2.5 mg / kg / 2 times a day according to the drug use instructions. On the 14th day of therapy increasing of viral load HHV-6B DNA detected in CSF (4 log10 copies / ml) and

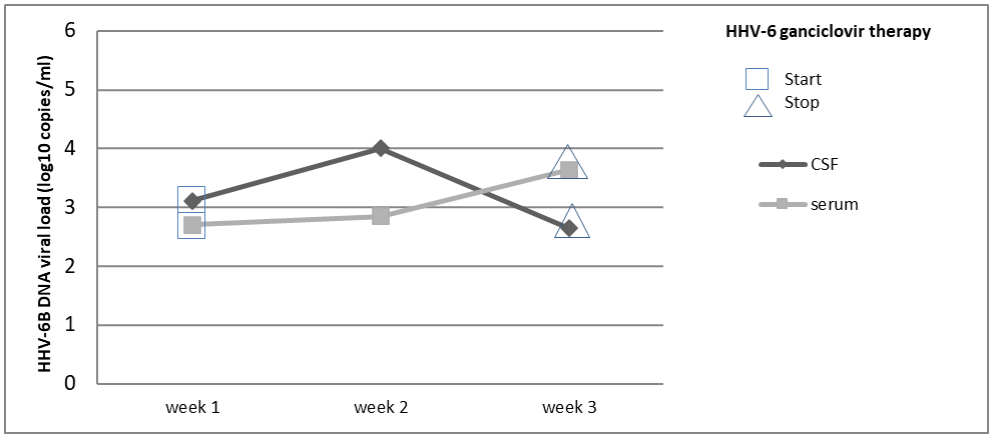

Figure 1. HHV-6B DNA viral loads in response to HHV-6 ganciclovir therapy

in serum (2.85 log10 copies / ml) in the absence of clinical manifestations **(Figure 1)**. The child was referred to pediatric infectious disease specialist. To confirm ci/iciHHV-6B repeated PCR performed. HHV-6B DNA detected in CSF (2.64 log10 copies / ml), in serum (3.64 log10 copies / ml), in peripheral blood mononuclear cells (PBMCs) (5.25 log10 copies / 105), in fingernails (77 597 copies / 105) and in hair follicles (82 572 copies / 105). In the similar biological material of the child's mother, no genetic markers of HHV-6B were detected. Father was not examined.

Taking into account absence of a decrease in the viral load, confirmed ci / iciHHV-6B, the normal condition of the child ganciclovir therapy was discontinued. The child was discharged from the hospital under the oncologist's follow up at the place of residence without any complaints. MRI monitoring of the brain and spinal cord was carried out in three months, complete remission of the underlying disease was confirmed; no changes characteristic of HHV-6 encephalitis were detected.

Discussion

The most frequent encountered issue associated with ci / iciHHV-6 positive individuals is the wrongful diagnosis of active HHV-6 infection. Patients with ci / iciHHV-6 have constant high levels of HHV-6 DNA, usually ≥ 106-107 copies / ml in case of viral reactivation absence (2, 11, 12). Depending on the type of tissue examined, the HHV-6 DNA copy number can vary greatly. It is considered that diagnosis of ci / iciHHV-6 is possible when the level of HHV-6 DNA in plasma is more than 3.5 log10 copies / ml, or more than 4 log10 copies / ml of CSF (5, 11, 13). Individuals with ci / iciHHV-6 have significantly higher viral DNA loads in PBMCs and whole blood (> 5.5 log10 copies / ml) than non-ci / iciHHV-6 individuals, even during primary HHV-6 infection in immunocompetent individuals or HHV-6 reactivations in immunosuppressed subjects (11). DNA PCR testing of hair follicles or fingernails can confirm ciHHV-6 status, because only ciHHV-6 individuals have detectable HHV-6 DNA in these tissues. Confirmation of iciHHV-6 can be made by testing the patient's parents or siblings, or sequential testing of the patient to demonstrate persistence of high HHV-6 DNA. For ciHHV-6, which is passed through the germline, at least one biological parent would carry ciHHV-6 (11, 12). In addition, ci / iciHHV-6 might induce the production of viral transcripts, proteins, and even transmissible virions, following reactivation (9, 14, 15). At a clinical level, this reactivation may be symptomatic or asymptomatic. In immunocompetent individuals, reactivation is usually asymptomatic or may lead to the development of organ-specific diseases (16, 17). Reactivations of HHV-6 are common in the post-transplantation period, although the frequency of reactivation may depend on the transplant type (2). In the post-transplant environment, HHV-6 infection can be pathogenic and cause encephalitis or bone marrow suppression (12). However, the frequency with which transplant recipients with ciHHV-6 can reactivate HHV-6 and develop complications is not clear, which makes it difficult to decide whether etiotropic therapy is necessary in case when a high viral load is detected (10).

Conclusion

The case report demonstrates the presence of ciHHV-6B in a child detected by screening for the infections on the background of chemotherapy. In this particular case, the viral load HHV-6B DNA in serum and CSF wasn't extremely high (2.7 log10 copies / ml; 3.11 log10 copies / ml, respectively). The treatment with ganciclovir did not significantly influence the reduction of the viral load HHV-6B DNA in serum and CSF and the course of the underlying disease. No adverse effects of antiviral treatment were registered. Taking into account the fact of the father's examination data absence (he does not reside in Belarus), it is difficult to say whether this form of infection is inherited (iciHHV-6) or de novo chromosomally integrated (after HHV-6 past infection).

Mistaking ci / iciHHV-6 for a marked reactivation of naturally-acquired infection can lead to unnecessary diagnostic procedures and treatments. The issue of chromosome integration of HHV-6 in immunocompromised patients requires special attention and further study.

Conflicts of Interest

Each author declares that he or she has no conflict of interest.

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