Meningoencephalitis Caused by Human Herpesvirus-6 in an Immunocompetent Adult Patient: Case Report and Review of the Literature

Summary: Human herpesvirus-6 (HHV-6) is the etiologic agent of roseola infantum, and has been implicated as a possible cause of encephalitis in pediatric and adult patients. A case of meningoencephalitis in an otherwise healthy, immunocompetent 59-year-old woman is described. The diagnosis of HHV-6 meningoencephalitis was confirmed by detecting viral DNA in cerebrospinal fluid collected in the acute stage of the disease by polymerase chain reaction. The patient was treated with acyclovir and recovered without any sequelae. The current knowledge of the pathophysiology, clinical course and outcome of HHV-6 meningoencephalitis in immunocompetent adult patients is also reviewed.

Introduction

Human herpesvirus-6 (HHV-6) was first isolated in 1986 from six patients with HIV-1 infection or with unrelated lymphoproliferative disorders [1]. Two variants of HHV-6 (HHV-6 A and HHV-6 B) have been identified, which may differ in their predilection to cause disease in children as compared to adults [2]. Although HHV-6 has been identified as the causal agent of exanthem subitum in children [3], primary infection can occur without a rash, as an afebrile illness with or without cervical lymphadenopathy [4]. As with other herpesviruses, HHV-6 persists in host cells in a latent state after the primary infection is resolved. The spectrum of disease caused by HHV-6 in immunocompetent adults ranges from mild mononucleosis-like illness to severe pneumonitis and fulminant hepatitis [5-7]. Since 1988 several studies have shown the association of HHV-6 in children with meningoencephalitis [8-13]. In 1994 Drobyisky et al. [14] first reported HHV-6 infection in an adult patient with encephalitis following bone marrow transplantation. HHV-6 also seems to be involved in the aetiology of multiple sclerosis (MS), inasmuch as higher average antibody titers to HHV-6 occur in patients with MS than in controls, and HHV-6 has also been detected by PCR in the cerebrospinal fluid of MS patients [15]. Several investigators have looked for evidence of HHV-6 involvement of the central nervous system (CNS) in both children and adults with AIDS [16-18]. As shown by epidemiologic studies, most persons are infected with HHV-6 at an early age. Consequently, primary infection of adults is relatively rare, whereas latent infection or reactivation is often noted in immunocompromised patients, especially in those with HIV-1 infection [19]. However, little is known about CNS involvement of HHV-6 in adult immunocompetent patients suffering from meningitis and/or encephalitis.

We report a case of meningoencephalitis caused by HHV-6 in an immunocompetent adult patient. An English-language literature search was performed using the MEDLINE data bases from 1966 through 1997, and the references of each article obtained from the literature search were reviewed for additional cases. Seventeen previously reported cases of meningitis or encephalitis caused by HHV-6 in adult immunocompetent patients were found.

Case Report

A 59-year-old woman with no significant medical history was admitted to the hospital because of suspected meningoencephalitis. The patient had been well until 15 days earlier, when malaise and low fever developed. Two days before admission, her condition suddenly worsened. Her temperature rose to 39.5°C, and she experienced diffuse headache, nausea, confusion, irritability and drowsiness. Findings on a cranial computed tomographic scan were reported to be normal, and an electroencephalogram showed diffuse slowing. Routine analysis of cerebrospinal fluid (CSF) revealed 14 white cells/mm³, with 60% lymphocytes and 40% granulocytes, a glucose level was 66 mg/dl, and the total protein level 93 mg/dl. Blood-brain barrier integrity, the Link and Tourtellotte IgG intrathecal synthesis indexes and the presence of IgG oligoclonal bands were evaluated using standard procedures. In the CSF of our patient we observed an alteration of blood-brain barrier integrity, and an increase above normal levels of both Tourtellotte and Link indexes, but no oligoclonal bands. All CSF and blood cultures for bacterial, fungal organisms were negative. Viral DNA of herpesvirus type 1 and type 2, varicella-zoster virus, cytomegalovirus, and Epstein-Barr virus were searched for in the CSF and in the peripheral blood mononuclear cells (PBMC) by using specific nested polymerase chain reaction (PCR) methods whose primers and protocols have been previously described [20]. DNA belonging to the major capsid protein gene of HHV-6 was searched for using the primers and PCR protocol previously described by Secchiere et al. [21]. HHV-6 was amplified by nested PCR in the CSF, but not in the PBMCs of the patient, whereas searching for the DNA of all other herpesviruses studied gave negative results. Intravenous acyclovir therapy (500 mg three times a day for 10 days) was begun.
immediately, and within the next 2 days the patient’s symptoms resolved with a return to normal mental status. The patient recovered from the disease without any sequelae and she was subsequently discharged.

Discussion

There are several reports of meningoencephalitis in children with primary HHV-6 infection [9, 22]. In addition, Caserta et al. [22] have shown that HHV-6 DNA can be detected in the CSF of children during and after the primary infection, and that HHV-6 shares neurotropic features with other herpesviruses, suggesting that the CNS could be a site of persistence or latency. There is increasing evidence for the frequent presence of HHV-6 in the CNS of AIDS patients [17, 18], inasmuch as levels of intrathecal antibodies to HHV-6 (IgM and IgG) were evaluated in 60% of patients with HIV-1 encephalopathy [23]. This suggests active and persistent HHV-6 infection of the CNS in many patients with HIV-1 encephalopathy. These studies suggest that HHV-6 in pediatric patients may invade the CNS directly during primary infection, whereas cases in adult patients with AIDS are consistent with HHV-6 reactivation in the CNS. The MEDLINE search for meningoencephalitis cases has shown that meningoencephalitis in immunocompetent subjects is less frequent than in children with primary infection or in adult patients with HIV-1 encephalopathy. There are only two studies which reported 17 of 188 (9%) cases of meningoencephalitis in adult immunocompetent patients. The first retrospective study [24] studied 138 patients. One group of 37 patients had previously undergone open brain biopsy for evaluation of encephalitis, while a second group of 101 patients with encephalitis had undergone prior PCR testing of CSF for herpes simplex virus. PCR results for herpes simplex virus were negative in all cases. Of the 138 patients, nine patients were positive for HHV-6 in CSF by PCR with HHV-6 specific primers. Two of nine were children, who may have had primary infection. No significant differences were found in the clinical findings, laboratory test results, CNS imaging or electroencephalographic studies between the nine patients with HHV-6-associated cases and the 129 without evidence for HHV-6 involvement. Clinical outcome in the nine HHV-6-positive patients included full recovery in four cases, mild to modest residual neurologic impairment in three, a persistent seizure disorder in one, and early death in one. These investigators stated that HHV-6 is associated with encephalitis of variable severity and that variant B is involved in some cases. The second study reported 10 of 50 (20%) adult immunocompetent patients with meningitis or encephalitis, who had increased intrathecal anti-HHV-6 early antigen IgM or IgG [23]. None of the control CSF specimens had IgM or IgG antibodies to HHV-6 early antigen. These results are consistent with active HHV-6 infection of the CNS in some cases of meningitis or encephalitis.

The percentage of children who are IgG-positive for HHV-6 increases gradually so that by the age of 13 months to 2 years most children (70%-83%) are seropositive, as are most adults [25]. Caserta et al. [22] have demonstrated that the presence of HHV-6 DNA in the CNS is associated with detection of HHV-6 DNA in peripheral blood mononuclear cells, and these investigators suggest that both peripheral blood mononuclear cells and the CNS may be reservoirs of latent or persistent HHV-6 infection. Although immunodepression, as noted in HIV-1-infected patients, may represent a significant factor in inducing reactivation of HHV-6 infection in the CNS, this is probably not true in adult patients with meningoencephalitis and without underlying immunodepression. In fact, the presence of HHV-6 DNA at autopsy in the brains of adult immunocompetent subjects, apparently free of clinical signs of viral infection and with no records of diseases associated with HHV-6, was clearly observed in 11 of 13 brain tissue specimens examined [26]. It should be noted that in our patient the presence of HHV-6 DNA was detected in the CSF but not in peripheral blood mononuclear cells. Since the majority of the population is exposed to HHV-6 in infancy, it may be postulated that meningoencephalitis in adult immunocompetent patients represents either secondary exposure to or reactivation of HHV-6. The in vitro data indicate greater susceptibility to HHV-6 to ganciclovir and foscarinet than acyclovir, which inhibited viral replication only at high concentrations [27, 28]. The efficacy of antiviral drugs in HHV-6 infection has not been evaluated in controlled clinical trials. However, our patient responded well to a 10-day course of treatment with acyclovir.

In conclusion, HHV-6 is associated with meningoencephalitis in adult immunocompetent patients. Since HHV-6 invades and may persist in the CNS, further work is needed to clarify the neuropathologic potential of HHV-6, both during and after primary infection, especially in adult patients with any clinical and humoral evidence of immunodepression.