Relapsing Herpes simplex virus encephalitis despite high-dose acyclovir therapy: a case report

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Central nervous system infection of Herpes simplex virus (HSV) is the most common etiologic agent of the non-epidemic fatal form of encephalitis. Relapse of HSV encephalitis is rare in childhood. In this report, we present our experience in a 36-month-old child with relapse of HSV encephalitis after 14-day acyclovir therapy.

A 36-month-old boy who was presented with deterioration in speech and motor functions and fluctuation of consciousness was treated with acyclovir for 14 days for HSV encephalitis. He was discharged since his cerebrospinal fluid findings returned to normal range and clinical improvement was seen. Ten days later, he was readmitted to our clinic with acute fever, focal convulsions and choreoathetoid movements, and altered consciousness. Acyclovir was started immediately, but he died on the 17th day because of respiratory failure.

Relapses due to HSV encephalitis are rare and limited to a small number of case reports in the literature. Persistence of HSV, detection of high viral load or detection of HSV by polymerase chain reaction, prior corticosteroid therapy, low total dosage of acyclovir (especially for children under 2 years of age) and short duration of therapy were suspected risk factors. Even absence of pleocytosis and normal cerebrospinal fluid biochemistry in our patient after treatment did not indicate eradication of HSV. In our opinion, treatment duration of HSV encephalitis, especially in small children, must be at least 21 days. Clinical and experimental studies are required since only case reports on this topic exist.

Key words: relapsing Herpes simplex virus encephalitis, encephalitis, acyclovir, childhood.

Central nervous system (CNS) infection of Herpes simplex virus (HSV) is the most common etiologic agent of the non-epidemic fatal form of encephalitis[1,2]. HSV infections of the CNS are among the most severe of all viral infections of the human brain. Acute febrile disease with decreased level of consciousness and focal neurological signs are the characteristic signs of HSV encephalitis[3].

Currently, HSE is estimated to occur in approximately 1 in 250,000 to 1 in 500,000 individuals per year[1,2]. Relapse of HSV encephalitis is rare in adults and only limited to a few case reports in childhood[4]. The mechanism of the relapse is not exactly clear, but detection of viral DNA and persistent immunohistochemical activity of HSV type 1 (HSV-1) in the brain suggest persistence of HSV replication following the recovery from encephalitis[5,6]. Additionally, most accused mechanisms are reactivation or re-infection of HSV and inadequate treatment, but no experimental data exist today regarding the exact mechanism.

We report our experience in a 36-month-old child with relapse of HSV encephalitis after 14 days of acyclovir therapy.

Case Report

A 36-month-old boy had an unremarkable medical history until presented with deterioration in speech and motor functions and fluctuation in consciousness lasting for more

than 10 days before admission to our hospital. A month before, he was admitted to another center with the complaints of fever, convulsions and fluctuation in consciousness. His magnetic resonance imaging (MRI) demonstrated increased signal on frontoparietal and parieto-occipital lobes on T_2–weighted images. Viral studies including serum HSV antibodies and cerebrospinal fluid (CSF) cultures were all negative; CSF analysis revealed an opening pressure of 21 mm CSF; glucose 73 mg/dl; protein 59 mg/dl and white blood cells (WBC) 120 cells/ml with 65% polymorphonuclear (PMN). Ceftriaxone was chosen as the initial treatment, and on the second day, the patient had focal convulsions and acyclovir was added to therapy empirically at the dose of 1500 g/m^2. The patient had clinical improvement and his follow-up lumbar puncture on the 15th day revealed normal CSF findings without leukocytosis. The patient was discharged with anti-epileptic drugs. Totally, he received acyclovir therapy for 14 days.

Ten days later, he was readmitted to our clinic with acute fever, focal convulsions and choreoathetoid movements and altered consciousness. His second MRI again demonstrated increased signal mainly at the bilateral frontoparietal lobes. His EEG demonstrated right-sided suppression in the background activity and slowing. On his second CSF examination, glucose was 61 mg/dl; protein was 28 mg/dl and there were no WBC. HSV-specific immunoglobulin IgM and IgG were both positive in CSF (98.4 ru/ml; positive cut-off: 1.3 ru/ml) and also CSF PCR was positive for HSV. He had developed status epilepticus resistant to phenytoin, phenobarbital and carbamazepine and his partial left-sided seizures did not respond even to general anesthesia. He died on the 17th day of admission because of respiratory failure.

Discussion

Our patient suffered from two apparent HSV-encephalitis episodes over a one-month period. In the first episode, diagnostic laboratory tests [including HSV polymerase chain reaction (PCR)] were not available, but the characteristic MRI images and clinical response to acyclovir therapy highly suggested active herpes encephalitis. The second and more severe attack resulted in death, and HSV infection was confirmed by positive serological tests and positive HSV PCR.

The average age of the recurrent HSV encephalitis patients reported in most of the case reports in the literature was under 36 months of age, and half of the relapses occurred within two weeks after ceasing the treatment of the first attack[4]. In relapse cases in the literature, acyclovir was started in an average of 4 days after the presentation of symptoms with the dose ranging from 12-60 mg/kg/day for 5 to 38 days[4]. Our patient was treated with relatively high dose (1500 g/m^2) of acyclovir for 14 days for the first attack and with the same dose until his death in the relapse of HSV encephalitis.

Relapse of HSV encephalitis in our patient was fatal despite a relatively high dose of acyclovir therapy. Fatality rate of HSV encephalitis is very high and in some articles complication and mortality rate due to HSV encephalitis reaches up to 84%[4].

Relapses due to HSV encephalitis are rare and limited to a small number of case reports in the literature. Although the exact mechanism for relapse of HSV encephalitis is not yet well established, HSV virus is known to be latent in the brain and to remain latent in the CNS even for 5-6 years, as proven by demonstration of DNA, nucleocapsid or antigens of HSV in samples provided by means of autopsy and biopsy[1,8]. Since HSV can remain latent after primary infection over one's lifetime, it is an expected fact that it could relapse.

The most commonly suspected mechanism of reactivation of HSV in relapsing HSV encephalitis is supported by recurrence of attack within 2-4 weeks after treatment[4]. In our case, CSF findings during the second attack suggested reactivation of HSV. Although there are cases with mononuclear pleocytosis (up to 128/mm^3) in CSF, some cases were reported with moderate pleocytosis. In our patient, despite disappearance of CSF pleocytosis after treatment with acyclovir in the first attack, relapse of HSV could not be prevented.

Persistence of HSV virus, detection of high viral load or positive HSV PCR, prior corticosteroid therapy, low total dosage of acyclovir (especially for children under 2 years of age) and short duration of therapy were suspected risk factors for relapses of HSV encephalitis.

The value of oral acyclovir as prophylaxis for herpetic CNS infections is also controversial. Determination of the risk factors is important

for deciding the total dosage and duration of acyclovir therapy in HSV encephalitis. For example, for neonatal HSV encephalitis, the currently recommended acyclovir dose and duration is 60 mg/kg/day intravenously divided into three doses for 21 days and 30 mg/kg/day for older children[9].

In conclusion, despite the advances in medicine, the exact mechanism and risk factors for HSV encephalitis are not well determined. Even the absence of pleocytosis and normal CSF biochemistry after treatment in our patient were not indicative of eradication of HSV. In our opinion, treatment duration of HSV encephalitis, especially in small children, must be at least 21 days. Clinical and experimental studies are required since only case reports on this topic exist.

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