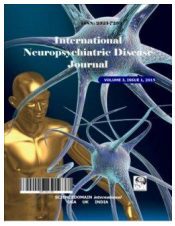

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Acute Human Herpesvirus-7-associated Encephalitis in a Young Adult Coinfected with Herpes Simplex Virus -1/2 and Epstein-Barr Virus

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Case Study

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ABSTRACT

Background: Herpesvirus encephalitis (HVE) is a serious threat to people's health and life. The most common cause of these is herpes simplex virus. On the contrary, only isolated cases of encephalitis associated with herpesvirus type 7 are described.
Objective: To describe a case of acute encephalitis in a young adult caused by uncommon Human herpesvirus 7 (HHV-7), underlying with Herpes simplex virus 1/2 (HSV-1/2) and Epstein-Barr virus (EBV) coinfection.
Results: A 20-years-old woman presented to The Center of Infectious Disorders of the Nervous System (Kyiv, Ukraine) after developing acute fever followed by a left side partial loss of hearing. Her physical examination showed slow mentation and generalized weakness. Cerebrospinal fluid (CSF) analysis revealed pleocytosis of 15 cell/µl (45% lymphocytes, 55% granulocytes), and HHV-7 DNA (3.35 log genome copies per ml). CSF also contained IgG antibodies against HSV-1/2 and EBV capsid antigen (CA). No HHVs DNA nor antibodies to viral proteins were detected in the blood. Areas of mild increased signal in parietal lobes were detected on an MRI brain scan. After treating with Ganciclovir the patient was discharged in good condition.
Conclusion: The author presents a case of primary HHV-7 infection followed acute encephalitis

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with typical MRI findings and HHV-7 DNA in CSF PCR. Ganciclovir therapy results in complete virology and neurological recovery. This case may be useful for clinicians in the differential diagnosis of CNS infection, taking into account that HHV-7 may be an etiological factor, and a timely diagnosis is the most important imperative for successful treatment.

Keywords: Encephalitis; human herpesviruses; human herpesvirus type 7.

1. INTRODUCTION

Encephalitis is a severe injury of the central nervous system, which may be induced by viruses as well as bacteria, fungi and parasites [1]. The most common cause of encephalitis is the viruses, especially herpesviruses(HVs). Human herpesviruses type 1,2,4,5,6 but not 7 are often detected at acute encephalitis [2,3]. These viruses are ubiquitous and infect 90% or more of the whole population in the first years of life. They have the ability to establish a lifelong latent infection in humans and to invade and replicate in the CNS. Apart from self-limited and relatively benign skin and mucosal infections, HVs may be the cause of serious diseases, particularly in immunocompromised individuals including potentially fatal viral encephalitis (HVE). The mortality rate associated with natural course of HVE is approximately 70% [4]. Despite antiviral therapy, the outcome is poor: mortality is still higher than 30%, and almost 60% of surviving individuals develop neurological sequelae. Preventive strategies are absent. It is suggested that direct virus-related and indirect immune-mediated mechanisms contribute to the lesions occurring in the CNS during HVE. We present here a case of acute encephalitis developed after primary HHV-7 infection.

2. CASE PRESENTATION AND DISCUSSION

A 20-years-old woman presented to The Center of Infectious Disorders of the Nervous System (Kyiv, Ukraine) in March 2017, following referral by the Institute of Otolaryngology. The patient was in good health until four months before admission to our clinic when she developed moderate grade fever (axillary temperature up to 39°C) followed by a left side partial loss of hearing. She was admitted to the local hospital where her fever and intoxication symptoms worsened during the next 2-3 days. After that the patient was transferred to the Institute of Otolaryngology for further management where she was treated with anti-inflammatory and neuroprotective drugs for 2 weeks. The general condition somewhat improved but hearing loss, weakness and sub febrile condition remained. Therefore she was sent to our center with the diagnosis of acute cochlear neuritis.

On admission, general condition was of moderate severity. Axillary temperature was normal. The patient was normotensive with pulse beats of 70 per minute. Her physical examination showed slow mentation along with generalized slowing of her responses to verbal commands and also generalized weakness. She was emotionally labile, good contact, well oriented, and answered the questions adequately. There was tremor in her hands during a Barre-probe. Lasseg, Nery, Gordon, Stryumpel, Sharapov-Raskolnikov, Chaddok, Pussep, and Babinsky symptoms were positive on one or both sides. Meningeal symptoms were not detected. She performed the coordination tests with intent, staggering in the Romberg pose.

A lumbar puncture was performed just on admission and CSF analysis revealed pleocytosis of 15 cell/μl (45% lymphocytes, 55% granulocytes). The protein and glucose levels were 0.16 g/L and 2.9 mmol/L respectively (the synchronous serum values were 69.4 g/L and 4.7 mmol/L). The CSF PCR was reported to be positive for HHV-7 DNA, containing 2230 genome copies per ml (gc/ml). Intrathecal synthesis of the IgG class antibodies against HSV-1/2 and VCA EBV were also revealed. No HHVs DNA or antibodies to viral proteins were detected in the blood. The patient's immune profile analysis showed a 2-fold increase in the level of cytotoxic CD8 T lymphocytes (47.1%) and a corresponding decrease in the immunoregulatory index (0.75). Bacterial culture of the CSF was sterile. MRI brain in T2W and FLAIR, but not T1W mode showed mild focal hyperintense lesions in the periventricular region of the parietal lobes, R > L which had no clear contours (Fig. 1). These changes can be interpreted as an inflammatory process.

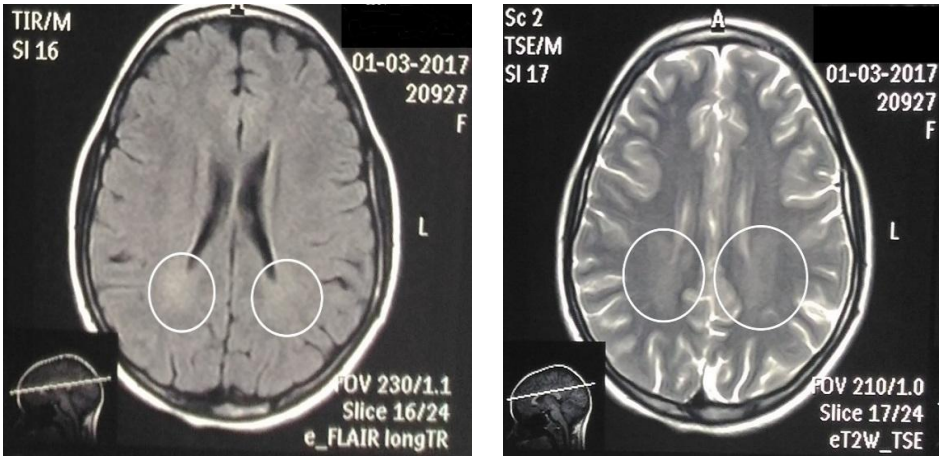

Fig. 1. FLAIR and T2 weighted images of MRI brain showing areas of mild increased signal in parietal lobes, R > L

She was treated with Ganciclovir sodium, 500 mg intravenous per day for 2 weeks, interferon α2b 3000000 IU per day for 2 weeks, and managed supportively with ademetionine, 400 mg, and citicoline, 1000 mg both intravenous daily. Control CSF analysis shown pleocytosis of 1 cell/μl (100% lymphocytes) and, the level of protein and glucose was 0.16 g/L and 3.1 mmol/L respectively. HHV-7 DNA was not found. She neurologically recovered and was discharged home in a stable condition without any neurological deficit. CSF analysis at 6 weeks after discharge did not detect either HHV-7 DNA or antibodies to VCA EBV while decreasing of anti-HSV IgG.

It is believed an acute encephalitis might occur either due to a primary infection in an immunocompetent individual or after becoming immunocompromised as a result of an underlying condition. Clinical and laboratory features of the primary infection are acute onset of neurological illness soon after the fever, wherein the acute samples may be either seronegative or have low avidity antibodies for the particular virus, but contained typically the viral DNA pinpointing the start of the primary infection [5,6]. It is this pattern that is observed in our patient. In accordance to the clinical practice guidelines of the Infectious Diseases Society of America [7], the presence of viral DNA in the patient's CSF accompanied by neurological disorders suggests HHV-7 as the possible cause of the encephalitis. Immunologic imbalance revealed in a patient is not the primary, but rather the result of a viral infection. Although the other two viruses, HSV-1/2 and EBV, are also in the productive phase of the life cycle, judging by the presence of IgG antibodies in CSF, no viral DNA was found in either blood or liquor. Apparently, not all virus functions express, themselves, no mature infectious viral particles can be produced. They most likely play an auxiliary role in encephalitis occuring. As a rule, mixed HVs infections of the CNS were reported in immunocompromised patients [8,9]. The patient described here had no history of being treated with immunosuppressive therapy. Although CSF had a fairly high cytosis, her blood examination showed normal cell count despite the presence of anti-VCA EBV IgG and anti-HSV-1/2 IgG in CSF, which is in accordance with the reported evidence for increased production of antibodies against several neurotropic pathogens including HSV-1/2, in the CSF of patients with bipolar disorder or autism spectrum disorders [10,11]. The absence of seizures and rough focal neurological signs characteristic of Herpes simplex encephalitis (HSE) confirm a mild process flow in the patient. It is well known HHVs encephalitis in immunocompetent individuals are usually mild including absent to moderate pleocytosis [12]. In contrast, Herpesvirus infection in immunocompromised patients was featured with more severe clinical manifestations [8].

Human herpesvirus 7 (HHV-7) is a member of the genus of the *Roseolavirus* of the subfamily *Betaherpesvirinae* and is closely related to HHV-6A and HHV-6B. HHV-7 exhibits a wide cell tropism *in vivo* and, like other herpesviruses, induces a lifelong latent infection in humans. HHV-7 is ubiquitous and is acquired, as usual, in childhood. Like HHV-6B, HHV-7 is highly

prevalent, with 75-90% of healthy adults harbouring the virus [13]. Recently it has been shown that HHV-7 DNA, like HHV-6B DNA, has a noticeable difference with respect to other HHVs, it may covalently integrate into the telomeric region of cell chromosomes including the germ-line cells in part of the general population. This means that the virus can be transmitted vertically, i.e. to offspring. It is assumed HHV-7 has been implicated in the pathogenesis of some neurological diseases, however, the virus is found in only a minority of patients. There is a single report of primary HHV-7 encephalitis in an immunocompetent adult, in whom HHV-7 DNA was found in the CSF [14], and another report of meningitis and optic neuritis resulting from reactivation of HHV-7 in a stem cell transplant recipient [15]. HHV-7 infection in children has been linked with seizures and encephalitis through the detection of intrathecal synthesis of antibodies against the virus [16]. The diagnosis of HHV-7 infection is performed by both serologic and direct methods. The most prominent technique is the quantification of viral DNA in CSF, blood and organs by means of real-time PCR. The prescribed treatment proved to be quite effective and resulted in complete recovery.

3. CONCLUSION

We present a case of acute encephalitis in a young adult caused by an uncommon Human herpesvirus 7 underlying HSV-1/2 and EBV coinfection.

CONSENT

Written informed consent was obtained from the patient for publication of this paper and accompanying images.

ETHICAL APPROVAL

Authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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