Journal of NeuroVirology (2023) 29:346–349
https://doi.org/10.1007/s13365-023-01127-1

CASE REPORT

Meningitis associated with HHV-7 in an Iranian immunocompetent adolescent girl

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Received: 20 January 2023 / Revised: 21 February 2023 / Accepted: 13 March 2023 / Published online: 22 May 2023

Abstract
There is limited literature regarding meningitis associated with HHV-7. This article reports an immunocompetent adolescent girl who developed fever, headache, and meningism which CSF molecular analysis with PCR was positive only for HHV-7. Interestingly, persistent cavum septum pellucidum and cavum vergae were observed on brain magnetic resonance imaging. The patient received antibiotics, dexamethasone, and acyclovir and then she gained full recovery. HHV-7 is a rare and yet possible pathogen in patients with meningitis, and this is the first described case report from Iran.

Keywords Human herpes virus 7 · HHV-7 · Meningitis · Iran

Background

Human herpes virus 7 (HHV-7) is a beta herpes virus and has a double-stranded DNA genome. It was isolated first from the $CD4^+$ T cells of a healthy person in the 1990s (Frenkel et al. 1990). This virus commonly infects $CD4^+$ T-lymphocytes and less commonly $CD8^+$ and immature T-cells (Berneman et al. 1992). Primary infection with this virus often occurs in infancy between two and five years old, and as a result, most adults are seropositive (Wyatt et al. 1991). Its reactivation is possible, however, has been reported mostly among immunocompromised individuals (Haidar 2020).

HHV-7 infection is associated with several clinical manifestations especially in childhood (Schwartz et al. 2014). It can cause an exanthem subitem similar to HHV-6 (Tanaka et al. 1994) or febrile illness without rash (Ward 2005). Neurological manifestations caused by HHV-7 have been reported in some studies, including febrile seizure (Caserta et al. 1998) and encephalopathy (Schwartz et al. 2014). A few articles have reported meningitis due to HHV-7 (Schwartz et al. 2014), as the following case, which describes a young girl with meningitis associated with this virus according to the case report guideline (CARE) (Gagnier et al. 2013).

Case description

A 17-year-old female presented to the emergency department with a fever of four days duration, frontal and temporal headache, and neck stiffness with no significant medical and drug history. Eight days ago, she had an aphthous ulcer in her mouth, and then maculopapular rashes appeared on her chest. The rashes were painless, without burning or itching, and they disappeared after a day. She had no complaints of vertigo, nausea, and vomiting. She was fully vaccinated, even for corona virus disease 2019 (COVID-19).

On physical examination, she had a heart rate of 130 beats/minute, blood pressure of 120/70 mmHg, and a temperature of 38.6 °C. At the time, no skin lesion or aphthous ulcer was observed. Bilateral cervical lymphadenopathy was noticed without any tenderness or warmness with an

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approximate diameter of 1.5 cm with a soft consistency. The cardiorespiratory examination was normal, and there was no abdominal organomegaly. Unilateral papilledema (+ 0.5) was observed with fundoscopy in the right eye. Kerning and Brudzinski tests were negative. There was no other lateralized neurological deficit.

Initial laboratory findings revealed the following: white blood cell (WBC) count 6.39 * 10^3/mm^3 (normal value: 4–10.9 * 10^3/mm^3) with 58.5% polymorphonuclear (PMN) and 32.1% lymphocytes, C-reactive protein (CRP) 2.7 mg/l (normal value: 0–6 mg/l), erythrocyte sedimentation rate (ESR) 25 mm/hour (normal value: up to 15 mm/hour), rheumatoid factor 4.3 IU/ml (normal value: up to 20 IU/ml), Wright antigen test 1/20 titer (normal value: less than 1/80 titer), Coombs Wright 1/40 titer (normal value: less than 1/80 titer), Widal antigen test negative, C3 131 mg/dl (normal value: 75–135 mg/dl), C4 31(normal value: 9–36 mg/dl), CH50 90% (normal value: less than 90%), anti-nuclear antibody negative (normal value: up to 1/40 titer), and anti-Smith antibody 0.1 Au/ml (normal value: up to 10 Au/ml). Peripheral blood smear was normal. Serological tests were negative for toxoplasma and Epstein–Barr virus (EBV). Polymerized chain reaction (PCR) was negative for influenza A and COVID-19.

Lumbar puncture was performed on the first day of hospitalization with an opening pressure of 24 mmHg. The CSF analysis showed WBC 30 count/ml (normal value: 0–5 count/ml) (PMN = 70% and lymphocytes = 30%), RBC 80 count/ml, glucose 52 mg/dl (normal value: 50–80 mg/dl) (blood glucose at the same time: 89 mg/dl), and protein 35.5 mg/dl (normal value: 15–40 mg/dl). CSF smear revealed no bacteria in gram stain, and CSF culture was reported negative.

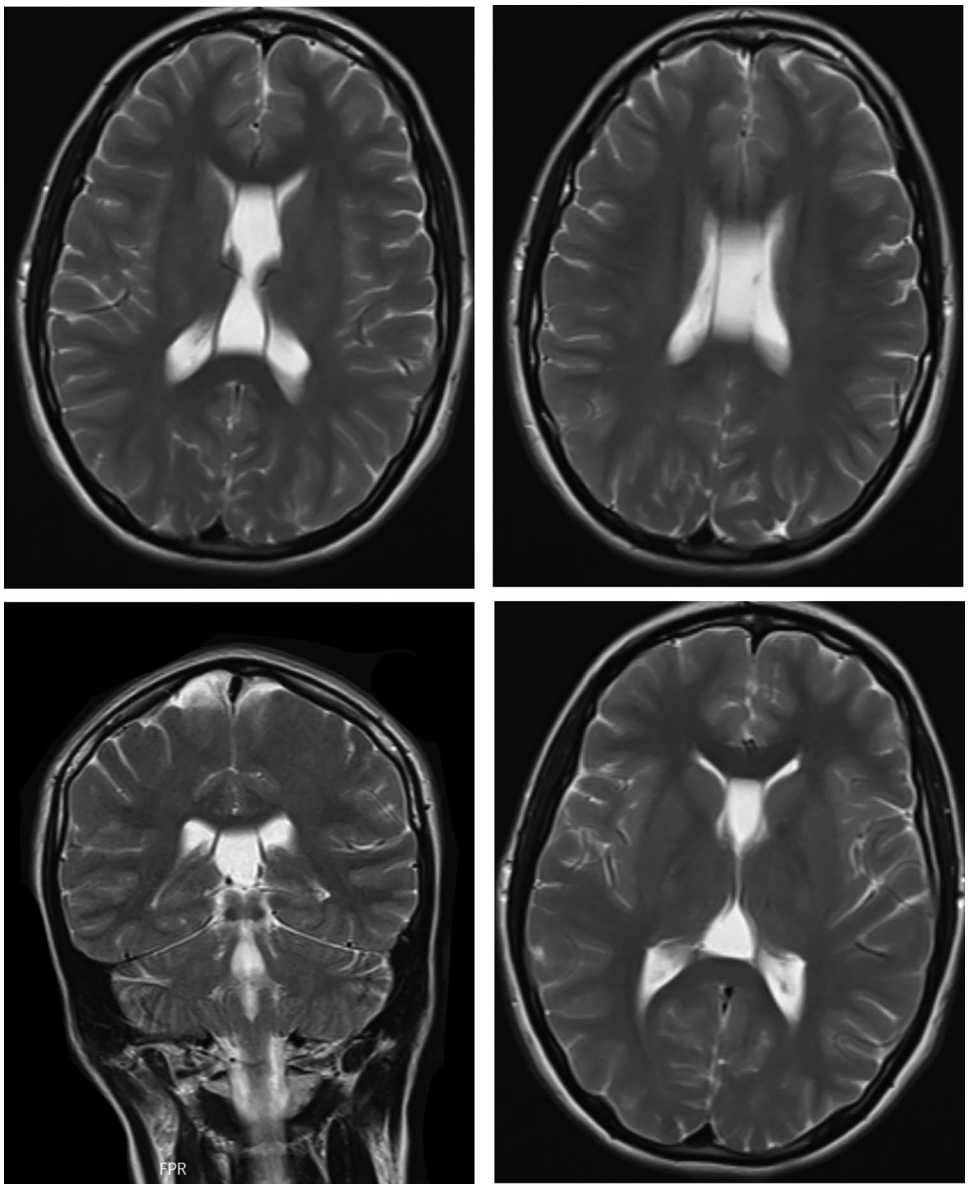

Fig. 1 Persistent cavum septum pellucidum and cavum vergae on brain MRI, coronal, and sagittal views

Sonography of cervical chain lymph nodes demonstrated reactive lymph nodes of lateral sides (right 19 mm, left 16 mm). Another oval-shaped reactive lymph node was noticed on the posterior side with a hypoechoic cortex and echogenic fatty hilum (right 21 mm, left 23 mm). Abdominal sonography was normal.

Neurocranium magnetic resonance imaging (MRI) did not show any evidence of encephalitis. Only persistent cavum septum pellucidum and cavum vergae were seen as it is shown in Fig. 1. Electroencephalogram, electrocardiogram, and echocardiography were reported normal.

The result of CSF molecular analysis on day three was positive only for HHV-7. It was negative for all of the following pathogeneses: *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus pneumonia*, *Streptococcus agalactiae*, *Listeria monocytogenes*, *Cryptococcus neoformans*, *Treponema pallidum*, *Mycobacterium tuberculosis* complex, *Coxiella burnetii*, *Borrelia burgdorferi*, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), Varicella-Zoster virus (VZV), EBV, cytomegalovirus (CMV), human herpesvirus VI (HHV 6), and human herpesvirus VIII (HHV 8).

The initial treatment included vancomycin, ceftriaxone, and dexamethasone for the first three days. On the third day, based on the positive PCR for HHV-7, acyclovir (500 mg every eight hours) was added to the treatment regimen. On the fourth day, treatment was continued with vancomycin, meropenem, and acyclovir to the end of day nine, and other drugs were discontinued.

The second LP was performed on day four since the fever was persistent. The opening pressure was 20, and fluid analysis revealed: WBC 5 counts/ml (normal value: 0–5 count/ml), RBC 2 counts/ml, glucose 5 mg/dl (normal value: 50–80 mg/dl), and protein 18.4 mg/dl (normal value: 15–40 mg/dl). The CSF molecular analysis was repeated, and it was positive for HHV-7 again.

The headache and fever were discontinued after five and six days respectively. The fundoscopy was repeated on day three which did not show any papilledema. Lymphadenopathy was significantly reduced by day seven. On day ten, the patient had no complaints and was discharged without any further treatment. In follow-up at the clinic one week after being discharged, she remained symptom-free. Lymphadenopathy was fully resolved, and laboratory data were reported normal after one month of follow-up.

Discussion and conclusion

Reports of meningitis with HHV-7 infection are limited in the literature, especially among the immunocompetent population. To the best of our knowledge, this was the first described meningitis associated with HHV-7 from Iran. Although one study done by Ebrahimi Taj et al. (2012) in Tehran, investigated HHV-6 and HHV-7 infection among admitted children with CNS infection (including both encephalitis and meningitis), it could not be concluded that any meningitis was associated with HHV-7. It was reported that two out of 150 total CSF samples were positive for HHV-7 (Ebrahimi Taj et al. 2012).

The presented case had papilledema which recovered eventually. A study by Yoshikawa et al. in 2003 in Japan reported a 9-year-old boy with meningitis and bilateral optic neuritis. He received allogeneic stem cell transplantation from his brother because of acute lymphoblastic leukemia. The PCR test for HHV-7 was positive. Aseptic meningitis recovered with supportive care; however, methylprednisolone was given for optic neuritis (Yoshikawa et al. 2003). In our case, dexamethasone was administered until day four which reaped fundoscopy did not show any papilledema.

Some other limited retrospective studies have reported positive HHV-7 PCR among patients with meningitis in different age groups. For instance, the newly published article by Okur et al. in Turkey has reported eight patients with meningitis whose CSF analysis showed HHV-7 infection. Interestingly, two cases had autoimmune diseases in follow-up including periodic fever, aphthous stomatitis, pharyngitis, adenitis, and juvenile idiopathic arthritis (Okur et al. 2022). Additionally, another case report described the association between sarcoidosis and HHV-7 infection. It may suggest the obscure possibility of autoimmunity caused by HHV-7 (Martikainen et al. 2013). Our case complained of an aphthous ulcer but had no other complaint or abnormality at the time of physical examination. Also, preliminary paraclinical tests to point out autoimmune diseases were negative.

Surprisingly, the MRI showed cavum septum pellucidum and cavum vergae which the patient, and her parents were not informed before about it. Cavum septum pellucidum is the normal variant of CSF between the two leaflets of the septum pellucidum, while cavum vergea is the posterior extension of it. Cavum septum pellucidum and cavum vergae may persist into adulthood in approximately 20 and one percent of individuals respectively (Tubbs et al. 2011). As far as our search result showed, there has been no association between HHV-7 with these two normal variations.

Unfortunately, it was not possible to use serology tests for HHV-7 detection. The study of Yoshikawa et al. (2000) used both serology and molecular analyses, and concluded that all meningitis associated with HHV-7 in adults was not due to primary infection by the virus (Yoshikawa et al. 2000). Although some articles have reported that supportive therapy would be enough to resolve full recovery, the effective treatment for HHV-7 is considered ganciclovir and foscarnet (Haidar 2020). These drugs were not available in our hospital as well as serology tests; therefore, treatment was continued with acyclovir, and it ended in full recovery. Anyhow, this case represents meningitis associated with HHV-7 infection,

and it may be of clinical importance as the first described case of Iran.

Author contribution M.S.F. and S.A.M. gathered data of the presented case and wrote the initial draft. H.Y. and M.A. made critical revision to the draft and made it finalized for the publication.

Availability of data and materials Data of the presented case may be available by asking the corresponding author.

Declarations

Ethical approval Informed consent was obtained from the parents to publish the case report.

Competing interests The authors declare no competing interests.

References

Berneman ZN, Ablashi DV, Li G, Eger-Fletcher M, Reitz MS Jr, Hung C-L et al (1992) Human herpesvirus 7 is a T-lymphotropic virus and is related to, but significantly different from, human herpesvirus 6 and human cytomegalovirus. Proc Natl Acad Sci 89(21):10552–10556

Caserta MT, Hall CB, Schnabel K, Long CE, D'Heron N (1998) Primary human herpesvirus 7 infection: a comparison of human herpesvirus 7 and human herpesvirus 6 infections in children. J Pediatr 133(3):386–389

Ebrahimi Taj F, Noorbakhsh S, Monavari H, Tabatabaie A (2012) Searching for the human herpes 6, 7 (PCR) in CSF of children admitted to the pediatric ward of Hazrat Rasool Hospital of Tehran. Avicenna J Clin Med 18(1):37–41

Frenkel N, Schirmer EC, Wyatt LS, Katsafanas G, Roffman E, Danovich RM et al (1990) Isolation of a new herpesvirus from human CD4+ T cells. Proc Natl Acad Sci 87(2):748–752

Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D et al (2013) The CARE guidelines: consensus-based clinical case reporting guideline development. J Med Case Reports 7(1):223

Haidar G (2020) HHV-6, HHV-7, and HHV-8: forgotten viruses in transplantation. Emerg Transp Infect Clin Chall Impli 1–27

Martikainen MH, Grönroos JO, Vuorinen T (2013) Detection of human herpesvirus 7 DNA from the CSF in association with neurosarcoidosis. J Med Virol 85(11):1935–1939

Okur DŞ, Ümran P, Güngör O, Öner SZ (2022) Evaluation of pediatric patients with human herpes virus-6 and/or human herpes virus-7 detected in cerebrospinal fluid: a single center experience. Pamukkale Tıp Dergisi 15(3):13

Schwartz KL, Richardson SE, Ward KN, Donaldson C, MacGregor D, Banwell B et al (2014) Delayed primary HHV-7 infection and neurologic disease. Pediatrics 133(6):e1541–e1547

Tanaka K, Kondo T, Torigoe S, Okada S, Mukai T, Yamanishi K (1994) Human herpesvirus 7: another causal agent for roseola (exanthem subitum). J Pediatr 125(1):1–5

Tubbs RS, Krishnamurthy S, Verma K, Shoja MM, Loukas M, Mortazavi MM et al (2011) Cavum velum interpositum, cavum septum pellucidum, and cavum vergae: a review. Childs Nerv Syst 27(11):1927–1930

Ward K (2005) The natural history and laboratory diagnosis of human herpesviruses-6 and-7 infections in the immunocompetent. J Clin Virol 32(3):183–193

Wyatt LS, Rodriguez WJ, Balachandran NT, Frenkel N (1991) Human herpesvirus 7: antigenic properties and prevalence in children and adults. J Virol 65(11):6260–6265

Yoshikawa T, Ihira M, Suzuki K, Suga S, Matsubara T, Furukawa S et al (2000) Invasion by human herpesvirus 6 and human herpesvirus 7 of the central nervous system in patients with neurological signs and symptoms. Arch Dis Child 83(2):170–171

Yoshikawa T, Yoshida J, Hamaguchi M, Kubota T, Akimoto S, Ihira M et al (2003) Human herpesvirus 7-associated meningitis and optic neuritis in a patient after allogeneic stem cell transplantation. J Med Virol 70(3):440–443