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# Evaluation of pediatric patients with Human Herpes Virus-6 and/or Human Herpes Virus-7 detected in cerebrospinal fluid: a single center experience

## *Beyin omurilik sıvısında Human Herpes Virus-6 ve/veya Human Herpes Virus-7 saptanan çocuk hastaların değerlendirilmesi-tek merkez deneyimi*

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**Abstract**

**Purpose:** Human Herpes Virus-6, is a common cause of febrile seizures in infancy and has been associated with meningitis in this age group. Human Herpes Virus-7, may also cause meningitis in children. The role and frequency of HHV-6 and HHV-7 in children's central nervous system diseases is unclear and is an area of ongoing research. In our study, we aimed to contribute to the literature about effects of Human Herpes Virus-6 and Human Herpes Virus-7 in central nervous system infections, in children.

**Materials and methods:** A retrospective study was conducted between March 2021 and March 2022. The study included children diagnosed with central nervous system infection and those found to have Human Herpes Virus-6 and or Human Herpes Virus-7 in their cerebrospinal fluid by multiplex real-time polymerase chain reaction.

**Results:** In our study, 86 children were hospitalized with the diagnoses of central nervous system infection. We detected Human Herpes Virus-6 and/or Human Herpes Virus-7 in cerebrospinal fluid in 12 (13.9%) children. When the patients were grouped according to their age, 75% were under the age of 2 years. Seizure was the presenting complaint in all patients with Human Herpes Virus-6 and 50% patients with Human Herpes Virus-7. Although the frequency of seizures was lower in the Human Herpes Virus-7, 75% of the seizures in this group were status epilepticus. Cerebral venous thrombosis was observed in 3 patients. All patients with thrombosis were found to be infected with Human Herpes Virus-7.

**Conclusio**n: Our study findings show that Human Herpes Virus-6 and Human Herpes Virus-7 may be associated with central nervous system infections and severe neurological diseases in childhood. Our study makes an important contribution to the literature in this respect and shows the need for multicenter prospective studies.

**Key words:** Human Herpes Virus-6, Human Herpes Virus-7, meningitis, children, seizure.

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**Öz**

**Amaç:** Ekzantem subitum'un etiyolojik ajanı Human Herpes Virus-6, bebeklik döneminde ateşli nöbetlerin yaygın bir nedenidir ve bu yaş grubunda menenjit ile ilişkilendirilmiştir. Human Herpes Virus-7'de çocuklarda ekzantem subitum ve ateşli nöbetlerle ilişkili olup menenjite de neden olabilir. Human Herpes Virus-6 ve Human Herpes Virus-7'nin merkezi sinir sistemi hastalıklarındaki rolü ve sıklığı belirsizdir ve devam eden bir araştırma alanıdır. Çalışmamızda Human Herpes Virus-6 ve Human Herpes Virus-7 etkenlerinin çocukluk çağı merkezi sinir sistemi enfeksiyonlarındaki etkileri konusunda literatüre katkı sağlanması amaçlanmıştır.

**Gereç ve yöntem:** Çalışmamıza Mart 2021-Mart 2022 tarihlerinde, merkezi sinir sistemi enfeksiyonu öntanıları ile yatırılan, beyin omurilik sıvılarında polimeraz zincir reaksiyonu ile Human Herpes Virus-6, Human Herpes Virus-7 saptanan çocuk hastalar alındı. Çalışmaya dahil edilen hastaların epidemiyolojik, klinik, laboratuvar bulguları, tedavileri ve prognozları incelendi.

**Bulgular:** Çalışmamızda toplam 86 çocuk merkezi sinir sistemi enfeksiyonu öntanıları ile yatırıldı. Merkezi sinir sistemi enfeksiyonu öntanısı ile yatırılan çocuklardan 12'sinde (%13,9) beyin omurilik sıvısında polimeraz zincir reaksiyonu ile Human Herpes Virus-6 ve/veya Human Herpes Virus-7 saptandı. Hastaların 9'u (%75) iki yaş altındaydı. Nöbet Human Herpes Virus-6 ile enfekte olanların tümünde, Human Herpes Virus-7 ile enfekte olanların 4'ünde (%50) başvuru yakınmasıydı. Nöbet sıklığı Human Herpes Virus-7 grubunda daha az olmasına

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rağmen bu grupta nöbetlerin %75'i status idi. Kraniyal manyetik rezonans görüntüleme ile 3 hastada serebral venöz tromboz görüldü. Tromboz saptanan hastalarının tümünün Human Herpes Virus-7 ile enfekte olduğu saptandı.
**Sonuç:** Çalışmamızdan elde edilen sonuçlar Human Herpes Virus-6 ve Human Herpes Virus-7 etkenlerinin çocukluk çağında merkezi sinir sistemi enfeksiyonları ve ağır nörolojik hastalıklar ile ilişkili olabileceğini göstermektedir. Çocuklarda Human Herpes Virus-7 ilişkili vaskulopatiler, otoimmun ve otoinflamatuar süreçler ile ilgili henüz yeterli sayıda veri bulunmamaktadır. Çalışmamız bu açıdan literatüre önemli bir katkı sağlamakta, çok merkezli ve ileriye yönelik çalışmalar yapılması gerekliliğini göstermektedir.

**Anahtar kelimeler:** Human Herpes Virus-6, Human Herpes Virus-7, menenjit, pediatri, nöbet.

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## Introduction

The brain parenchyma is surrounded by three membranes: dura mater, arachnoid mater, and pia mater. Infection of the brain parenchyma is called "encephalitis", whereas infection of the meninges is called "meningitis". Infection of both is called "meningoencephalitis". Bacterial meningitis is less common with the use of conjugate vaccines. However, aseptic meningitis is more common, and viruses play a major role. The incidence of viral meningitis ranges from 10 to 20 cases per 100.000 children per year [1-4].

The incidence is highest in infants under 1 year of age. A second peak is seen in children over 5 years of age [3, 4]. In temperate climates, most cases occur in summer and autumn [5-7].

All members of the Herpesviridae family can cause viral meningitis; however, herpes simplex viruses are classically associated with neurological infection. Human herpes virus-6 (HHV-6) is a member of the Herpesviridae family. HHV-6 infects most children in the first 2 years of life [4, 5]. Primary HHV-6 infection often presents as a febrile illness without rash. Sometimes the rash occurs typically immediately after the fever has subsided. HHV-6, the etiologic agent of roseola or exanthema subitum, is a common cause of febrile seizures in infancy and has been associated with meningitis in this age group [8, 9].

Human herpes virus-7 (HHV-7), which is also associated with exanthema subitum and febrile seizures in infancy, may also cause meningitis in children. However, HHV-7 infection is usually asymptomatic. Infection with HHV-7 usually occurs in childhood but peaks at a later age than infection with HHV-6, usually around 3 years of age [10, 11]. An association between HHV-7 and febrile seizures is reported [9-11]. The role and frequency of HHV-6 and HHV-7 in children's central nervous system (CNS) diseases is unclear and an area of ongoing research.

In our study, we investigated the epidemiology and the course of CNS infection due to HHV-6 and/or HHV-7 in children followed up between March 2021 and March 2022. We aimed to contribute to the literature about roles and effects of HHV-6 and HHV-7 in CNS infections, in children, with the light of the findings of our study.

## Materials and methods

A retrospective study was conducted at the Pamukkale University Faculty of Medicine Department Pediatric Infectious Diseases and Pediatric Neurology between March 2021 and March 2022. The study included children diagnosed and hospitalized with CNS infection and those found to have HHV-6 and or HHV-7 in their cerebrospinal fluid (CSF) by multiplex real-time polymerase chain reaction (PCR) (FTD Neuro9, Fast Track Diagnostics, Lüksemburg) method.

This study was approved by Medical Ethics Committee, Non-Invasive Clinical Research Ethics Committee of Pamukkale University Faculty of Medicine and conducted in accordance with the Declaration of Helsinki. Written informed consent to participate in the study was obtained from the patients enrolled or their parents.

SPSS (Statistical Package for the Social Sciences) 23.0 software (IBM SPSS Statistics, IBM Corporation) was used for performing chi-square test, Student's *t*-test, and Mann-Whitney *U*-test; $p<0.05$ was considered to indicate a significant difference.

## Results

In our study, 86 children were hospitalized with the diagnoses of CNS infection in Pamukkale University Faculty of Medicine, Pediatric Infectious Diseases and Pediatric Neurology services. Of these eighty-six patients, 15 had viral meningitis. Multiplex real-time PCR detected HHV-6 (n=4, 4.6%) and/or HHV-7 (n=8, 9.3%) in CSF in 12 (13.9%) children hospitalised with the diagnosis of CNS infection.

### Demographic features

The study included 5 (41.7%) girls and 7 (58.3%) boys, with a mean age of 39.5±56.1 months (median age, 13 months; range, 1-192 months). When the patients were grouped according to their age, 9 (75%) were under the age of 2 years, and 6 of them were 1 year old or younger (Table 1). One of the other 3 children was 16 years old (Table 1). The mean age of the patients with HHV-6 in CSF was 8.9±5.9 months (median, 8.9 months; range, 1-14 months), and the mean age of patients with HHV-7 was 54.8±64.2 months (median, 19.5 months; range, 11-192 months). No statistically significant difference was found between the children with HHV-6 and HHV-7 in terms of gender ($p$=0.58) and age ($p$=0.19). When the seasonal distribution of the patients was examined, 8 (66.7%) were hospitalised in January-February, 3 (25%) in October-November, and 1 in May (Table 1).

**Table 1.** Summary of Cases

| No of Cases | Age (mo) | Sex | Season | HHV type | CNS symptoms | Cranial MRI |
|---|---|---|---|---|---|---|
| 1 | 14 | G | Winter | HHV-6 | Seizure, unconsciousness, | Normal |
| 2 | 84 | B | Winter | HHV-7 | Headache | Cerebral ven thrombosis |
| 3 | 11 | B | Autumn | HHV-7 | Seizure | Normal |
| 4 | 9 | G | Autumn | HHV-6 | Seizure | Normal |
| 5 | 1 | B | Winter | HHV-6 | Seizure, unconsciousness | - |
| 6 | 192 | G | Autumn | HHV-7 | Headache | Normal |
| 7 | 16 | G | Spring | HHV-7 | Unconsciousness | Normal |
| 8 | 12 | B | Winter | HHV-6 | Seizure | Normal |
| 9 | 23 | B | Winter | HHV-7 | Seizure (status), unconsciousness | Cerebral ven thrombosis |
| 10 | 88 | B | Winter | HHV-7 | Headache, unconsciousness | Cerebral ven thrombosis |
| 11 | 12 | G | Winter | HHV-7 | Seizure (status), unconsciousness | Normal |
| 12 | 12 | B | Winter | HHV-7 | Seizure (status), unconsciousness | Normal |

Mo: months, HHV: human herpes virüs, G: girl, B: boy, CNS: central nervous system

### Clinical findings

Among the complaints of children, fever was reported in all patients. Headache was reported in 3 (25%), vomiting in 5 (41.2%), convulsions in 8 (66.7%), and unconsciousness in 7 (58.3%) patients. The mean number of days with fever was 2.75±1.8 (median, 2; range, 1-7) days.

When patients were grouped according to HHV types, headache was reported in 3 (37.5%) patients with HHV-7. Seizure was the presenting complaint in all patients with HHV-6 and 4 (50%) patients with HHV-7. Although the frequency of seizures was lower in the HHV-7 group, 75% of the seizures in this group were status epilepticus. Status epilepticus was not observed in patients with HHV-6.

Physical examination revealed fever in all patients, nuchal rigidity in 9 (75%) patients, and altered consciousness in 7 (58.3%) patients. In addition, 1 patient had fontanel bulge and pulsation, 1 had exudative crypt in the tonsils, and 1 had swelling and limitation of movement in the right knee. Fontanel bulge and pulsation was accepted as a significant and positive examination finding for meningitis because it was accompanied by fever, projectile vomiting, seizure, restlessness, and nuchal rigidity, and no other condition was found to explain.

The mean body temperature, of the patients were 38.8±0.5 (median, 39; range 38-39.5)°C.

**Laboratory and radiological findings**

When the complete blood count tests of the patients included in the study were examined, 8 (66.7%) had leucocytosis, none of them had leukopenia, platelet values were within normal ranges in all, 9 (75%) were anaemic, mean hemoglobin values were 11.3±1.2 (median, 11.2; range 9.2-13.4) g/dL, respectively. The mean CRP level was 65.2±92.3 (median, 5.1; 0.2-212) mg/L, and it was elevated in 7 (58.3%) patients.

In CSF examinations obtained by lumbar puncture, 70 leukocytes per $mm^3$ were seen in 1 patient, and no cells were seen in the others. Four patients (33.3%) had high CSF protein, and none of the patients had CSF glucose lower than 50% of the serum glucose value. Mean CSF protein was 0.75±1.25 (median, 0.28; 0.11-4.42) g/L, mean CSF glucose was 66.3±16.2 (median, 60; 46-92) mg/dL. There was no growth in the CSF culture of any patient, and no bacteria were detected by PCR. BOS PCR analysis of children included in our study detected HHV-7 in 8 patients (66.7%) and HHV-6 in 4 patients (33.3%).

In order to detect other foci that may accompany meningitis that may cause fever in patients younger than two years of age, and to exclude vasculopathy and autoinflammatory conditions that may involve lungs in 3 children older than two years of age, chest radiographs were taken for all patients. Chest radiographs of all patients were normal.

Cranial MRI was performed in 2 of our patients because of severe headache, in 3 patients because they had focal seizures, and in 6 patients because of unconsciousness. Cranial magnetic resonance imaging (MRI) was performed in all but 1 patient, and cerebral venous thrombosis was observed in 3 (27.2%) patients. All patients with thrombosis were found to be infected with HHV-7. The frequency of cerebral vein thrombosis in patients with HHV-7 was 37.5%.

**Treatment and prognosis**

During the follow-up, 4 patients needed intensive unit care. These patients were followed up in the intensive care unit for an average of 6.25±3.95 (median, 5; range 3-15) days. HHV-6 was found in 1 (25%), and HHV-7 was found in 3 (75%) of those who needed intensive care. The mean hospital stay of the patients included in the study was 9.83±8.94 (median, 8.5; range, 3-35) days.

The mean hospital stay was 6.25±5.85 (median, 3.5; range, 3-15) days in patients with HHV-6 and 11.63±9.99 (median, 9; range, 3-35) days in patients with HHV-7, and no statistically significant difference was observed ($p$=0.35). Ganciclovir was administered to a patient with sepsis and a 1-month-old patient with a history of prematurity whose seizures could not be stopped.

Other patients did not receive antiviral treatment. In the follow-up, 1 patient with exudative tonsillitis was evaluated as having HHV-7 meningitis and PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis) attack, and 1 patient with swelling in the right knee and limitation of movement was evaluated as having HHV-7 meningitis and oligoarticular JIA (juvenile idiopathic arthritis) attack. LMWH (low molecular weight heparin) was started in patients with cerebral vein thrombosis on cranial MRI, and their thrombosis regressed in the follow-up. No patient died, and all patients were discharged without sequelae.

**Discussion**

The rate of detection of HHV-6 and/or HHV-7 in the CSF of children hospitalised in our centre with diagnoses of CNS infection was 13.9%, which was similar to the frequency reported in the literature [11, 12]. Although it varies according to season, geography, and age, the frequency of HHV-6 and/or HHV-7 in CNS infections is reported to be between 14% and 17% in the literature [11, 12]. Of the patients included in our study and followed up during our study, 4.6% were infected only with HHV-6 and 9.3% with only HHV-7. These two agents were not detected together in any patient. The rate of detection of HHV-6 in the CSF of children is reported in the range of 0.3-32% in the presence of sepsis, seizures, and neurological findings with fever and in the range of 3.3-4.2% in the presence of meningitis [11-25]. HHV-7 is a rare aetiological agent in CNS infections in children, the rate of detection in CSF varies between

1% and 14.8%, and its incidence increases especially with increasing age [11, 12, 16, 22, 25-35].

The mean age of the patients included in our study was 39.5±56.1 months (median, 13 months; range, 1-192 months), and 75% of them were under 2 years of age, similar to the age of patients reported in the literature. There was no statistically significant difference in age between children with HHV-6 and HHV-7 ($p$=0.19). However, the mean age and median age of patients with HHV-7 were higher than those in patients with HHV-6. The median age of children with CNS infection and HHV-7 detected in the CSF are reported to be higher than those in patients with HHV-6 [12, 24, 28, 36, 37]. In addition, the detection of HHV-7 in 3 children older than the others brings to mind that HHV-7 reactivation may have developed in these children. It has been reported in the literature that reactivation of HHV-7 is seen rather than primary infection in adults [11, 12, 16, 22, 24-37].

Contrary to what is reported, most of our patients were hospitalized during the winter months. Cases of meningitis caused by HHV-7 and/or HHV-6 are reported in spring and summer months, and those of HHV-6 in the autumn months [38].

Regarding the clinical findings of our patients, complaints and examination findings were not different from those reported in the literature. However, the absence of febrile status epilepticus (FSE) in patients with HHV-6 differed what is reported in the literature. HHV-6 is also reported as an important causative factor of FSE, and in one study it was responsible for 32% of all FSE cases [11-25].

When laboratory findings were examined, leucocytosis was more common than leukopenia, and the mean CRP value was high, which is expected in bacterial infections and not in viral infections. In addition, the frequency of detection of thrombosis in the cerebral veins in our patients infected with HHV-7 was different what is reported in the literature in terms of HHV-7-related vasculopathies in the paediatric age group [26, 39, 40]. The detection of HHV-7 in CSF PCR in all patients with cerebral thrombosis was another important finding. While HHV-7-related cerebral vasculopathies are reported in adults, there is not enough data in children [26, 32, 29-40]. Our study makes an important contribution to the literature in this respect.

In CSF examinations obtained by lumbar puncture, 70 leukocytes per $mm^3$ were seen in 1 patient, and no cells were seen in the others. In viral meningitis, the leukocyte count in CSF is usually found to be between 10-500 cells/$mm^3$. However, increased leucocyte counts cannot be seen in CSF in meningitis caused by enteroviruses, parechoviruses and rarely human herpes viruses especially early in the course of infection [41-43]. In addition, the small number of leukocytes in the CSF of our patients may have been lysed until the microscopic examination.

HHV-7-infected patients needed intensive care more frequently, and these patients stayed longer, but not significantly, in the hospital than patients infected with HHV-6. These findings suggest that HHV-7 causes more severe disease and CNS involvement. Primary infection of HHV-7 at a young age is reported to often cause mild symptoms and clinical pictures, but if it is diagnosed at an older age, it causes severe neurological pictures such as encephalitis and encephalopathy [11, 12, 16, 22, 24-37].

The development of a PFAPA attack in one of our patients infected with HHV-7 and the development of an oligoarticular JIA attack in another patient raises the possibility that this virus may also be associated with autoimmune and autoinflammatory processes. HHV-7-related autoimmune vasculopathies and events are also mentioned in the literature [12, 24, 26, 31, 32, 39-40]. Our study contributes to the literature in terms of raising awareness about HHV-7-related vasculopathies and autoimmune processes and highlights the need for multicentre and prospective studies.

The main limitation of our study is the low number of patients with HHV-6 and/or HHV-7 detected in the CSF. However, when the pre-pandemic two-year period and the 1-year pandemic period before our study were compared, CSF was obtained from a total of 165 children, and HHV-6 and/or HHV-7 were detected by PCR in only 12 of 165 CSF samples. It was determined that these 12 patients were those included our study. Another important

limitation is the retrospective analysis of the cases. Therefore, a prospective multicentre study is necessary.

In conclusion, our study findings show that HHV-6 and HHV-7 can cause CNS infections and severe neurological diseases in childhood. The frequency of HHV-7 and the severity of its neurological findings increase with age. Although HHV-6 is an important cause of FSE, HHV-7 can also result in the same picture. HHV-7 should also be considered in the etiology of children presenting with FSE.

There is not enough data on HHV-7-related vasculopathies and autoimmune and autoinflammatory processes in children. Our study makes an important contribution to the literature in this respect and shows the need for multicentre prospective studies.

**Conflict of interest:** No conflict of interest was declared by the authors.

## References


1. Michos AG, Syriopoulou VP, Hadjichristodoulou C, et al. Aseptic meningitis in children: analysis of 506 cases. PLoS One 2007;2:674. https://doi.org/10.1371/journal.pone.0000674
2. Martin NG, Iro MA, Sadarangani M, Goldacre R, Pollard AJ, Goldacre MJ. Hospital admissions for viral meningitis in children in England over five decades: a population-based observational study. Lancet Infect Dis 2016;16:1279-1287. https://doi.org/10.1016/S1473-3099(16)30201-8
3. Hviid A, Melbye M. The epidemiology of viral meningitis hospitalization in childhood Epidemiology 2007;18:695. https://doi.org/10.1097/ede.0b013e3181567d31
4. Centers for Disease Control and Prevention (CDC). Outbreaks of aseptic meningitis associated with echoviruses 9 and 30 and preliminary surveillance reports on enterovirus activity-United States, 2003. MMWR Morb Mortal Wkly Rep 2003;52:761-764. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5232a1.htm. Accessed August 15, 2003
5. Nigrovic LE. Aseptic meningitis Handb Clin Neurol 2013;112:1153-1156. https://doi.org/10.1016/B978-0-444-52910-7.00035-0
6. Bronstein DE, Glaser CA. Aseptic meningitis and viral meningitis. In: Feigin and Cherry's textbook of pediatric infectious diseases, 8th, Cherry JD, Harrison GJ, Kaplan SL, Steinbach WJ, Hotes PJ (Eds), Elsevier, Philadelphia 2019:355.
7. Cassady K, Gnann JW, Whitley RJ. Viral infections of the central nervous system. In: Therapy of Infectious Diseases, Baddour L, Gorbach S (Eds), WB Saunders, Philadelphia 2003:237.
8. Abedi GR, Watson JT, Nix WA, Oberste MS, Gerber SI. Enterovirus and Parechovirus Surveillance - United States, 2014-2016. MMWR Morb Mortal Wkly Rep 2018;67:515-518. https://doi.org/10.15585/mmwr.mm6718a2
9. Rotbart HA. Viral meningitis and the aseptic meningitis syndrome. In: Infections of the Central Nervous System, 2nd ed, Scheld MW, Durack WR (Eds), Lippincott Raven, Philadelphia 1997:23.
10. Caserta MT, Hall CB. Human Herpes-6. In: Infections of the Central Nervous System, 2nd ed, Scheld MW, Durack WR (Eds), Lippincott Raven, Philadelphia 1997:129.
11. Yoshikawa T, Ihira M, Suzuki K, et al. Invasion by human herpesvirus 6 and human herpesvirus 7 of the central nervous system in patients with neurological signs and symptoms. Arch Dis Child 2000;83:170-171. https://doi.org/10.1136/adc.83.2.170
12. Ward KN, Andrews NJ, Verity CM, Miller E, Ross EM. Human herpesviruses-6 and -7 each cause significant neurological morbidity in Britain and Ireland. Arch Dis Child 2005;90:619-623. https://doi.org/10.1136/adc.2004.062216
13. Ansari A, Li S, Abzug MJ, Weinberg A. Human herpesviruses 6 and 7 and central nervous system infection in children. Emerg Infect Dis 2004;10:1450-1454. https://doi.org/10.3201/eid1008.030788
14. Caserta MT, Hall CB, Schnabel K, McIntyre K, Long C, Costanzo M, Dewhurst S, Insel R, Epstein LG. Neuroinvasion and persistence of human herpesvirus 6 in children. J Infect Dis 1994;170:1586-1589. https://doi.org/10.1093/infdis/170.6.1586
15. Kondo K, Nagafuji H, Hata A, Tomomori C, Yamanishi K. Association of human herpesvirus 6 infection of the central nervous system with recurrence of febrile convulsions. J Infect Dis 1993;167:1197-1200. https://doi.org/10.1093/infdis/167.5.1197
16. Torigoe S, Koide W, Yamada M, Miyashiro E, Tanaka Taya K, Yamanishi K. Human herpesvirus 7 infection associated with central nervous system manifestations. J Pediatr 1996;129:301-305. https://doi.org/10.1016/s0022-3476(96)70259-7
17. Suga S, Yoshikawa T, Asano Y, et al. Clinical and virological analyses of 21 infants with exanthem subitum (roseola infantum) and central nervous system complications. Ann Neurol 1993;33:597-603. https://doi.org/10.1002/ana.410330607
18. Hall CB, Long CE, Schnabel KC, et al. Human herpesvirus-6 infection in children: a prospective study of complications and reactivation. N Engl J Med 1994;331:432-438. https://doi.org/10.1056/NEJM199408183310703

19. Kleines M, Scheithauer S, Schiefer J, Häusler M. Clinical application of viral cerebrospinal fluid PCR testing for diagnosis of central nervous systemdisorders: a retrospective 11-year experience. Diagn Microbiol Infect Dis 2014;80:207-215. https://doi.org/10.1016/j.diagmicrobio.2014.07.010

20. Messacar K, Breazeale G, Wei Q, Robinson CC, Dominguez SR. Epidemiology and clinical characteristics of infants with human parechovirus or human herpes virus-6 detected in cerebrospinal fluid tested for enterovirus or herpes simplex virus. J Med Virol 2015;87:829-835. https://doi.org/10.1002/jmv.24119

21. Wada K, Mizoguchi S, Ito Y, et al. Multiplex real-time PCR for the simultaneous detection of herpes simplex virus, human herpesvirus 6, and human herpesvirus 7. Microbiol Immunol 2009;53:22-29. https://doi.org/10.1111/j.1348-0421.2008.00090.x

22. Säll O, Thulin Hedberg S, Neander M, et al. Etiology of central nervous system ınfections in a rural area of nepal using molecular approaches. Am J Trop Med Hyg 2019;101:253-259. https://doi.org/10.4269/ajtmh.18-0434

23. Huang LM, Lee CY, Lee PI, Chen JM, Wang PJ. Meningitis caused by human herpesvirus-6. Arch Dis Child 1991;66:1443-1444. https://doi.org/10.1136/adc.66.12.1443

24. Epstein LG, Shinnar S, Hesdorffer DC, et al. Human herpesvirus 6 and 7 in febrile status epilepticus: the FEBSTAT study. Epilepsia 2012;53:1481-1488. https://doi.org/10.1111/j.1528-1167.2012.03542.x

25. Parisi SG, Basso M, Del Vecchio C, et al. Virological testing of cerebrospinal fluid in children aged less than 14 years with a suspected central nervous system infection: a retrospective study on 304 consecutive children from January 2012 to May 2015. Eur J Paediatr Neurol 2016;20:588-596. https://doi.org/10.1016/j.ejpn.2016.04.002

26. Schwartz KL, Richardson SE, Ward KN, et al. Delayed primary HHV-7 infection and neurologic disease. Pediatrics 2014;133:1541-1547. https://doi.org/10.1542/peds.2013-3344

27. Van der Berg JS, van Zeiji JH, Rotteveel JJ, Melchers WJ, Gabreels FJ, Galama JM. Neuroinvasion by human herpesvirus type 7 in a case of exanthem subitum with severe neurologic manifestations. Neurology 1999;52:1077-1079. https://doi.org/10.1212/wnl.52.5.1077

28. Caserta MT, Hall CB, Schnabel K, Long CE, D'Heron N. Primary human herpesvirus 7 infection: a comparison of human herpesvirus 7 and human herpesvirus 6 infection in children. J Pediatr 1998;133:386-389. https://doi.org/10.1016/s0022-3476(98)70275-6

29. Teach SJ, Wallace HL, Evans MJ, Duffner PK, Hay J, Faden HS. Human herpesviruses types 6 and 7 and febrile seizures. Pediatr Neurol 1999;21:699-703. https://doi.org/10.1016/s0887-8994(99)00068-5

30. Pohl Koppe A, Blay M, Jager G, Weiss M. Human herpes virus type 7 DNA in the cerebrospinal fluid of children with central nervous system diseases. Eur J Pediatr 2001;160:351-358. https://doi.org/10.1007/s004310100732

31. Corral Í, Sainz de la Maza S, Rodríguez M, Kawiorski MM, López Martínez MJ, Galán JC. Molecular detection of human herpesvirus 7 DNA in cerebrospinal fluid from adult patients with neurological disorders. J Neurovirol 2018;24:333-338. https://doi.org/10.1007/s13365-018-0618-4

32. Ward KN. The natural history and laboratory diagnosis of human herpesviruses-6 and -7 infections in the immunocompetent. J Clin Virol 2005;32:183-193. https://doi.org/10.1016/j.jcv.2004.11.008

33. Tanaka K, Kondo T, Torigoe S, Okada S, Mukai T, Yamanishi K. Human herpesvirus 7: another causal agent for roseola (exanthem subitum). J Pediatr 1994;125:1-5. https://doi.org/10.1016/s0022-3476(94)70113-x

34. Torigoe S, Kumamoto T, Koide W, Taya K, Yamanishi K. Clinical manifestations associated with human herpesvirus 7 infection. Arch Dis Child 1995;72:518-519. https://doi.org/10.1136/adc.72.6.518

35. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47:303-327. https://doi.org/10.1086/589747

36. Hall CB, Long CE, Schnabel KC, et al. Human herpesvirus-6 infection in children. A prospective study of complications and reactivation. N Engl J Med 1994;331:432-438. https://doi.org/10.1056/NEJM199408183310703

37. Agut H, Bonnafous P, Gautheret Dejean A. Human Herpesviruses 6A, 6B, and 7. Microbiol Spectr 2016;4:DMIH2-0007-2015. https://doi.org/10.1128/microbiolspec.DMIH2-0007-2015

38. Zeytinoğlu A, Erensoy S, Sertöz R, et al. Santral sinir sistemi enfeksiyonlarında viral etiyolojinin İzmir'de bir üniversite hastanesinin yedi yıllık verileri üzerinden değerlendirilmesi. Mikrobiyol Bul 2017;51:127-135. https://doi.org/10.5578/mb.53825

39. Gray PE, O'Brien TA, Wagle M, et al. Cerebral vasculitis in X-Linked lymphoproliferative disease cured by matched unrelated cord blood transplant. J Clin Immunol 2015;35:604-609. https://doi.org/10.1007/s10875-015-0194-9

40. Steininger J, Rossmanith R, Geier CB, et al. Case report: meningoencephalitis with thrombotic occlusive vasculopathy in a young ebv-naive boy is associated with a novel *SH2D1A* mutation. Front Immunol 2021;12:747738. https://doi.org/10.3389/fimmu.2021.747738

41. Simko JP, Caliendo AM, Hogle K, Versalovic J. Differences in laboratory findings for cerebrospinal fluid specimens obtained from patients with meningitis or encephalitis due to herpes simplex virus (HSV) documented by detection of HSV DNA. Clin Infect Dis 2002;35:414-419. https://doi.org/10.1086/341979

42. de Crom SC, van Furth MA, Peeters MF, Rossen JWA, Obihara CC. Characteristics of pediatric patients with enterovirus meningitis and no cerebral fluid pleocytosis. Eur J Pediatr 2012;171:795-800. https://doi.org/10.1007/s00431-011-1626-z

43. Yun KW, Choi EH, Cheon DS, et al. Enteroviral meningitis without pleocytosis in children. Arch Dis Child 2012;97:874-878. https//doi.org/10.1136/archdischild-2012-301884

### Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee, Non-Invasive Clinical Research Ethics Committee of Pamukkale University Faculty of Medicine (date of approval 08/02/2022 and 03 approval number)

### Author contributions

Conceptualization: D.S.O.; investigation: D.S.O., Ü.P., S.Z.Ö.; methodology: D.S.O.; project administration: D.S.O., Ü.P.; writing-original draft: D.S.O., Ü.P.; treatment: D.S.O., O.G., Ü.P. In addition, all authors discussed the entire study and approved the final version.