Cite as: Gołuchowska N, Mejer-Zahorowska A, Pogonowska M, Piwowarczyk A, Kuchar E, Kalicki B: Dilemmas in HHV-6-associated neurological diseases. Pediatr Med Rodz 2024; 20 (4): 449–454

Natalia Gołuchowska[1], Agnieszka Mejer-Zahorowska[1], Milena Pogonowska[1,2], Anna Piwowarczyk[3], Ernest Kuchar[3], Bolesław Kalicki[1,2]

Received: 06.10.2024
Accepted: 25.11.2024
Published: 10.04.2025

Dilemmas in HHV-6-associated neurological diseases

Dylematy diagnostyczne w neuroinfekcjach wywołanych przez HHV-6

[1] Department of Paediatrics, Paediatric Nephrology and Allergology, Military Institute of Medicine – National Research Institute, Warsaw, Poland
[2] Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland
[3] Department of Observation and Isolation and Paediatrics, University Clinical Centre of the Medical University of Warsaw, Warsaw, Poland
Correspondence: Natalia Gołuchowska, Department of Paediatrics, Paediatric Nephrology and Allergology, Military Institute of Medicine – National Research Institute, Szaserów 128, 04-349 Warsaw, Poland, e-mail: goluchowskan@gmail.com

https://doi.org/10.15557/PiMR.2024.0070

ORCID iDs
1. Natalia Gołuchowska https://orcid.org/0000-0002-1928-175X
2. Agnieszka Mejer-Zahorowska https://orcid.org/0009-0008-7842-2007
3. Milena Pogonowska https://orcid.org/0000-0002-7031-8538
4. Anna Piwowarczyk https://orcid.org/0000-0002-8764-7442
5. Ernest Kuchar https://orcid.org/0000-0002-7883-2427
6. Bolesław Kalicki https://orcid.org/0000-0003-1606-5100

Abstract

Infections with human herpesvirus type 6 commonly affect children up to 3 years of age. The infection is usually mild, however, severe cases involving the central nervous system can occur. We conducted a retrospective analysis of three cases who tested positive for human herpesvirus type 6 in cerebrospinal fluid polymerase chain reaction. Symptoms, laboratory findings, and proposed management in cases of uncertain aetiology of the neuroinfection are discussed. Attention is also drawn to the controversies related to the interpretation of molecular findings due to the latency of human herpesvirus type 6 infection and the lack of treatment recommendations for encephalitis of the aforementioned aetiology. Management of severe cases is suggested, along with potential treatment options.

Keywords: encephalomyelitis, neuroinfection, encephalitis, human herpes virus type 6, HHV-6, roseola

Streszczenie

Zakażenia ludzkim wirusem *herpes* typu 6 są powszechne u dzieci do 3. roku życia. Przebieg zakażenia zwykle jest łagodny, chociaż zdarzają się ciężkie przebiegi z zajęciem ośrodkowego układu nerwowego. W pracy dokonano retrospektywnej analizy zachorowania trojga dzieci, u których wykryto materiał genetyczny ludzkiego wirusa *herpes* typu 6 w płynie mózgowo-rdzeniowym. Scharakteryzowano ich objawy, wyniki badań laboratoryjnych i zaproponowano postępowanie w przypadku wątpliwości co do etiologii neuroinfekcji. Zwrócono również uwagę na kontrowersje w związku z interpretacją wyników badań molekularnych z uwagi na latentność zakażenia tym wirusem. Zaproponowano postępowanie w przypadku ciężkiego przebiegu choroby i przedstawiono możliwości terapeutyczne.

Słowa kluczowe: zapalenie opon mózgowo-rdzeniowych, neuroinfekcja, zapalenie mózgu, ludzki wirus *herpes* typu 6, HHV-6, rumień nagły

INTRODUCTION

Human herpesvirus 6 (HHV-6) infections are common in children up to 3 years of age[1,2].

Primary HHV-6 infection is most often mild, biphasic, and manifests as exanthema subitum (ES, also known as roseola infantum). The first febrile phase lasts 3–5 days, and the second exanthematous phase, usually occurs after the fever subsides (Fig. 1)[3]. The classic ES develops in about 15% of infected children[4].

The infection may be additionally accompanied by neurological symptoms, such as febrile seizures or encephalitis in children up to 3 years of age, which, according to literature, is rarely observed in older children[5]. Neurological complications such as, among others, delayed psychomotor development and motor or cognitive disorders, have been observed after HHV-6 encephalitis in 50% of immunocompetent children[6,7].

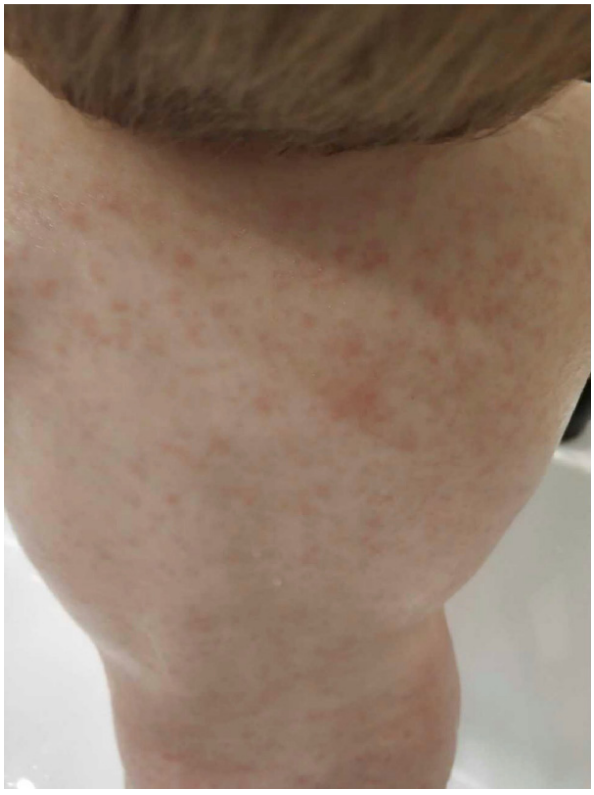

Fig. 1. Clinical image of skin lesions in the course of HHV-6 infection (exanthema subitum). Source: own resources

Major criterion: acute or subacute (<4 weeks) disturbance of consciousness/ change in personality/cognitive functions/coma ≥24 hours
Major criterion + 2 of the following (**possible** encephalitis) or ≥3 of the following (**probable or confirmed** encephalitis): · fever ≥38°C within 72 hours (before or after the onset of symptoms) OR infection · generalised or partial seizures (without previous epilepsy) · new, focal neurological symptoms · CSF pleocytosis ≥5 cells/µL · brain tissue damage (MRI/CT) · EEG abnormalities
CT – computed tomography; **CSF** – cerebrospinal fluid; **EEG** – electroencephalography; **MRI** – magnetic resonance imaging.

Tab. 1. Diagnostic criteria for encephalitis[9,10]

HHV-6 infection most often becomes latent and may reactivate in immunosuppressed individuals[1]. Studies have shown that HHV-6 reactivation may cause, among others, encephalitis in transplant recipients[8].

No therapeutic standards for HHV-6 neuroinfections have been established to date. This paper presents three cases of children who had HHV-6 genetic material detected in their cerebrospinal fluid (CSF). The children met the criteria for suspected meningitis/encephalitis proposed by Venkatesan et al., and later modified by the British group of researchers (Tab. 1)[9,10].

This paper describes the symptoms and laboratory findings observed in the affected children, as well as proposes a management strategy in the case of uncertain aetiology of neuroinfection. Treatment regimens used in each of the patients are also presented.

CASE 1

A nine-month-old male infant was admitted with suspected neuroinfection. The boy had a history of a week-long fever, with a tendency for increasingly shorter afebrile periods. Additionally, he developed isolated papular lesions on the lower legs and palms. When vomiting co-occurred, the child was admitted to hospital. Laboratory tests performed at that time showed no elevated inflammatory markers, with C-reactive protein (CRP) of 0.3 mg/dL (N <0.5 mg/dL), and a negative antigen test for influenza, COVID-19 and RSV. Due to persistent fever, cefuroxime was used empirically. However, the child's condition deteriorated during hospital stay. The boy experienced pathological sleepiness; according to his mother, he sat unsteadily and did not stand upright, despite having already mastered these skills. Due to suspected neuroinfection, lumbar puncture was performed. Clear CSF with lymphocyte differential (64%) and cytosis (76 cells/µL) was obtained.

Polymerase chain reaction (PCR) testing of the collected material detected HHV-6 DNA. Due to persistent quantitative disturbances of consciousness in the form of excessive sleepiness, electroencephalography (EEG) was done, which found no abnormalities. Antibiotic therapy was ceased and symptomatic treatment with antipyretics and adjuvant drip infusions was continued, achieving rapid improvement in the child's general condition. Imaging of the central nervous system (CNS) under general anaesthesia was not performed due to the risk of anaesthesia outweighing the benefits of the examination. On the day of discharge, the patient had slightly reduced muscle tone and increased tendon reflexes in the left lower limb. The child's behaviour and skills did not differ from before the illness. The boy sat confidently without support, walked on all fours and stood holding on to furniture. He was discharged home on day 5 of hospital stay in good

DOI: 10.15557/PiMR.2024.0070

general condition, with recommendations for further care in the neurological clinic.

CASE 2

A six-year-old boy was admitted to hospital due to seizures in the course of respiratory tract infection. The patient had developed fever and cough 4 days prior to admission. The fever subsided after 3 days, but vomiting, headache and drowsiness occurred. On the night before admission, his parents witnessed two episodes of convulsions/tremors of the limbs lasting up to 60 seconds. The boy, of Ukrainian origin, previously healthy, was not under the care of any specialist clinics.

On admission, the patient was in general average good condition, drowsy, but after waking up for the examination, he followed the instructions. Significant deviations from normal in physical examination included signs of mild dehydration, impaired nasal patency, thick fluid behind the tympanic membrane of the right ear, and a questionable symptom of neck stiffness. Laboratory tests performed at that time revealed leukocytosis with WBC of 27 thousand/μL, differential with a predominance of neutrophils (82.1%) and elevated inflammatory markers (CRP 12.0 mg/dL, N <0.5 mg/dL). Also, genetic material of rhinovirus was detected in the respiratory panel. In the first hours of hospital stay, the boy experienced a generalised seizure with urinary incontinence, which was stopped with rectal diazepam. Encephalitis was suspected, and acyclovir was started empirically. Brain computed tomography found no increased intracranial pressure, bleeding or focal lesions, and the fluid reserve was preserved. Lumbar puncture was then performed. CSF examination revealed cytosis with 273 cells/μL (neutrophils predominated in the differential), and HHV-6 genetic material was detected in PCR. The CSF PCR resulted in acyclovir discontinuation. EEG revealed a pharmacological sleep pattern without any detectable changes. Chest X-ray showed parenchymal densities. Based on laboratory workup, meningitis, pneumonia and otitis media were diagnosed. A 3% NaCl solution for inhalation and ceftriaxone were used. On the day that followed, three episodes of tonic-clonic seizures occurred, and the treatment was supplemented with intravenous levetiracetam and dexamethasone. Magnetic resonance imaging (MRI) of the brain was performed, showing mildly restricted diffusion in the right anteromedial midbrain. Confluent, ill-defined areas of clearly increased signal were detected bilaterally around the lateral ventricular triangles on T2-weighted/FLAIR sequences, without restricted diffusion or contrast enhancement. EEG showed significant generalised slowing.

On the days of hospital stay that followed, the child remained in a general moderately severe condition, with efficient circulatory and respiratory functions, a tendency to bradycardia, and quantitative disturbances of consciousness (short periods of consciousness, with transient verbal contact). Periodically, there were episodes of tension with accompanying upward turning of the eyeballs, without seizures in the follow-up EEG. Neurological consultation found abolished abdominal skin reflexes and bilaterally positive Babinski sign.

After a short period of improvement (the boy started sitting up, eating, with longer periods of activity and logical contact), the patient experienced qualitative disturbances of consciousness on day 8 of hospital stay (he "saw" a character from a fairy tale), and stopped speaking and responding to commands. Also, choreic movements involving the upper and (periodically) lower limbs, as well as bulbar symptoms were observed.

Pulse glucocorticoid therapy was initiated for 5 days, without significant improvement. A follow-up brain MRI performed on day 8 of hospital stay showed a picture comparable to the previous examination, while EEG showed improvement, with moderate generalised functional slowing. Serum IgM antibodies for tick-borne encephalitis were found during diagnostic workup. Serum anti-neuronal and anti-cerebellar antibodies were negative. Despite slight improvement in the general condition over the subsequent days of hospital stay, fluctuations in consciousness were observed: from significant slowing down with limited contact to hyperactivity with no logical contact. Laboratory findings revealed increased serum lactates and normal levels of ammonia. Due to the need to continue diagnosis for metabolic diseases and constant neurological care, the patient was transferred to a specialist centre.

CASE 3

A seven-month-old girl was admitted to the Department of Paediatrics due to a 3-day fever and a week-long respiratory infection. On admission, the child was in average general condition. Physical examination revealed redness and swelling of the eyelids, discharge in the nasal cavities and on the posterior wall of the pharynx, as well as bilateral rhonchi over the lung fields. Laboratory workup showed slightly elevated inflammatory markers (CRP 3.0 mg/dL, N <0.5 mg/dL). Nasopharyngeal PCR did not detect any genetic material of the tested bacteria and viruses. General urinalysis showed no signs of infection. Chest X-ray revealed bilateral perihilar peribronchial consolidations. Pneumonia was diagnosed. Intravenous amoxicillin with clavulanic acid and symptomatic treatment were started. A macular skin rash, typical of roseola, was observed after a dozen or so hours. Due to the child's average general condition with hyperesthesia and photophobia, inflammatory markers were measured and a decrease in CRP (1.1 mg/dL) was found, with high procalcitonin (2.37 ng/mL). Due to the lack of obvious clinical improvement on day 2 of hospital stay, lumbar puncture was performed, revealing increased CSF pressure. General CSF analysis did not reveal any significant abnormalities, while PCR detected HHV-6 genetic material. Blood, stool and CSF cultures were sterile.

 DOI: 10.15557/PiMR.2024.0070

No EEG abnormalities were found. Since the girl's neurological symptoms were gradually resolving, no CNS MRI under general anaesthesia was performed. Antibiotic therapy was continued, leading to improvement of the clinical condition and symptom resolution.

DISCUSSION

Primary HHV-6 infection usually presents as an acute, self-limiting illness of infancy and childhood[11,12]. Children under 3 years of age are mainly affected[13,14]. It is characterised by fever persisting for 1–5 days, followed by a pale pink, finely punctate rash that fades under pressure and persists for about 2 days[3,15].

Although HHV-6 infection is usually asymptomatic or mild, the CNS may get involved (meningitis or encephalitis) in some cases.

An analysis conducted in Japan demonstrated that the annual incidence of encephalitis/encephalopathy associated with ES was estimated at 60 cases, with an unfavourable prognosis[8]. Berzero et al. found HHV-6 in CSF in approximately 4.6% of patients, encephalitis during primary infection in 0.4%, and encephalitis due to viral reactivation in 0.8% of patients[5].

HHV-6 neuroinfections are increasingly common in immunosuppressed patients, but they can also occur in immunocompetent individuals[11–13,16].

It is worth mentioning that the cases described in this paper differed due to the age of the patients, presented symptoms and treatments used. Due to the lack of treatment standards for HHV-6 neuroinfections, the intensity and strategy of diagnosis and treatment were determined by the clinical condition of patients. The therapeutic regimens did not differ from the standards for other viral neuroinfections.

It should be emphasised that the diagnosis of HHV-6 infection primarily relies on molecular techniques, with serological methods used in the case of interpretation difficulties[17]. The diagnosis is confirmed mainly based on PCR gene amplification, which allows for detection and quantitative determination of the viral genome. Serological tests may be useful in differentiating primary infection from reactivation of the latent form[1].

Parameter	Patient 1	Patient 2	Patient 3
Colour	Clear	Clear	Clear
Transparency	Full	Full	Full
Protein	37.7 mg/dL (N: 15.0–45.0)	32.3 mg/dL (N: 15.0–45.0)	12.4 mg/dL (N: 20–40)
Glucose	51 mg/dL (N: 40–85)	64 mg/dL (N: 40–85)	60 mg/dL (N: 60–100)
Chlorides	122 mmol/L (N: 115–130)	121 mmol/L (N: 115–130)	127 mmol/L (N: 100–130)
Cytosis	76 cells/µL (N: 0–30)	273 cells/µL (N: 0–10)	1 cell/µL (N: 0–5)

Tab. 2. Comparison of cerebrospinal fluid parameters in the described patients

The analysis of general CSF findings in the described patients showed that increased CSF cytosis may develop in HHV-6 encephalitis (2 of 3 patients). The general CSF examination was normal in case 3 (Tab. 2). There is evidence in the literature that HHV-6 infects neuroglial cell lines and modulates cytokine synthesis in HHV-6-infected astrocyte cell line, therefore, like other herpesviruses, HHV-6 may remain latent throughout the patient's life after primary infection and reactivate in the event of impaired immune function. The pathogenesis of HHV-6 encephalitis, and in particular the difference between HHV-6 encephalitis at the time of primary infection and at the time of virus reactivation, remains unclear[6].

Berzero et al. confirmed the previous data indicating that, as far as immunocompetent patients are concerned, HHV-6 CNS involvement occurs in children under 3 years of age during primary infection, whereas in the group of non-immunocompetent patients, this complication is observed in adolescents and adults as a result of reactivated infection. This is particularly likely in the early period after bone marrow stem cell transplantation. Additionally, the cited authors assessed 926 patients, including 45 patients with HHV-6 DNA detected in CSF and/or blood: 17 immunocompetent patients (4 of whom were diagnosed with HHV-6 encephalitis; in all cases these were children under 3 years of age) and 28 non-immunocompetent patients (including 7 patients diagnosed with HHV-6 encephalitis, of whom only 2 belonged to the paediatric population and were adolescents). The disease was caused by virus reactivation in all non-immunocompetent patients.

Berzero et al. assessed CSF/blood HHV-6 viral load ratio. The HHV-6 CSF/blood viral load ratio was >1 in 6 of 7 non-immunocompetent patients and <1 in all 4 immunocompetent patients. The investigators suggested that a HHV-6 CSF/blood replication ratio >1 may suggest HHV-6 encephalitis in immunocompromised individuals[5].

The same researchers also assessed the correlation of clinical, radiological, and biological features with HHV-6-induced encephalitis in both immunocompetent and immunocompromised individuals. Encephalitis was diagnosed in 4 immunocompetent children <2 years of age. All of them presented with seizures or mild encephalopathy during primary HHV-6 infection. Among the immunocompromised patients, encephalitis was diagnosed in 7 children with a mean age of 14 years. The children presented with the following symptoms: mental disorders (7/7), seizures (3/7), behavioural disorders (2/7), hyponatremia (2/7), and anterograde amnesia (1/7). Abnormal MRI findings were obtained in 2 patients[5].

The cases presented in this paper concerned immunocompetent patients (Cases 1 and 3). In the second described case, it is not certain whether the six-year-old patient experienced reactivation of HHV-6 and encephalitis during co-infection with tick-borne encephalitis or whether other diseases, including metabolic disorders, were the underlying cause (the results are underway). However, the course of

DOI: 10.15557/PiMR.2024.0070

the illness in the second patient was severe and led to complications (epilepsy).

The available data suggest that encephalitis may develop as a complication of primary HHV-6 infection in children <3 years of age. In older children and adults, the presence of HHV-6 in CSF suggests reactivation of infection, which may occur under various pathological conditions. Hence, it should be emphasised that it is necessary to search for other etiological factors responsible for encephalitis, especially in immunosuppressed individuals. Therefore, the interpretation of CSF positivity for HHV-6 and the decision on further diagnosis and treatment should be cautious and take into account the medical history and clinical symptoms. Considering the above, despite detecting HHV-6 in CSF in the described case 2, other causes of encephalitis were sought[18].

MRI of the brain should be considered in all children with suspected encephalitis. In their study involving 54 children with HHV-6 encephalitis, Eliassen et al. found abnormal brain MRI in 65% of patients, with the most common pathological feature being restricted subcortical diffusion (62% of abnormal results), which is the earliest detectable abnormality occurring within 24 hours of encephalitis symptom onset[19].

Treatment of HHV-6 neuroinfections may be classified as targeted (antivirals) and adjuvant (glucocorticoids, mannitol, 3% hypertonic NaCl solution).

Immunocompetent children diagnosed with HHV-6 encephalitis are not conventionally treated with antivirals. Ganciclovir and foscarnet are used as targeted treatment (combined or separately) in the group of non-immunocompetent patients. Despite literature data suggesting that roseola infantum virus infection may be associated with an increased long-term risk of epilepsy or autoimmune encephalitis, there is currently insufficient evidence to support routine use of antivirals[19,20].

One of the patients described was put on high-dose glucocorticoids due to suspected autoimmune disease.

Hypertonic NaCl solution is most often used for cerebral oedema. There are studies in the literature comparing 3% hypertonic NaCl solution vs. 20% mannitol solution in viral neuroinfections. In their prospective study in 57 children, Rameshkumar et al. showed that hypertonic NaCl solution reduced intracranial pressure more effectively than mannitol. This trend was maintained beyond 72 hours[21].

CONCLUSIONS

Neurological diseases are a rare complication of HHV-6 infection. Every patient up to 3 years of age with an unclear clinical picture in the course of HHV-6 infection and neurological symptoms, even with normal CSF findings, should be suspected of having HHV-6 encephalitis.

Molecular testing of CSF collected by lumbar puncture is the basis for diagnosing neuroinfections. Interpretation of molecular tests may cause difficulties in determining whether HHV-6 is responsible for encephalitis in the course of primary infection, indicates latent infection (viral DNA detected in the course of another CNS disease) or reactivated infection in an immunosuppressed patient. In such cases, establishing the diagnosis requires a thorough analysis of the course of the disease, taking into account the patient's age, chronic diseases and epidemiological exposure. PCR of serum samples, brain MRI in the child, and exclusion of other causes that may have led to encephalitis or suggest its symptoms will also be helpful.

Therapy is symptomatic and involves anti-oedematous and antiviral agents. Due to the low quality of scientific evidence, no clear treatment guidelines have yet been developed.

Each patient with HHV-6 encephalitis should be put under the supervision of a neurologist and psychologist, especially due to motor and cognitive complications.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: MP, AP, EK. Collection, recording and/or compilation of data; analysis and interpretation of data: NG, AMZ, MP. Writing of manuscript: NG, AMZ. Critical review of manuscript: MP, AP, BK. Final approval of manuscript: BK.

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DOI: 10.15557/PiMR.2024.0070