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CASE REPORT

Neurological involvement of human herpesvirus type 7 in the pediatric population: a rare presentation of a known disease

Acometimento neurológico do herpesvírus humano tipo 7 na população pediátrica: apresentação rara de uma doença conhecida

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ABSTRACT

Introduction: Human herpesvirus type 7 (HHV-7) is a common virus that typically causes self-limited infections in children, rarely affecting the central nervous system. There is still limited information in the literature regarding the severity of neurological manifestations of the disease in children and its treatment. This study aims to describe five pediatric cases of neurological disease caused by HHV-7, with varying clinical presentations and courses, highlighting the main clinical and epidemiological features as well as the management provided. **Case Report:** Five immunocompetent patients, aged between ten months and eight years, were diagnosed with acute meningoencephalitis caused by HHV-7 through qualitative PCR testing of cerebrospinal fluid. Initial nonspecific symptoms included fever, flu-like symptoms, diarrhea, and vomiting, followed by neurological manifestations such as irritability, somnolence, seizures, strabismus, nystagmus, and cranial nerve palsies. None of the patients developed exanthema. Two patients progressed to shock or respiratory failure and required admission to the intensive care unit. A total of four patients received intravenous acyclovir, and two also received ceftriaxone. Two patients developed cerebral hypoxia and were left with neurological sequelae, while three were discharged with complete resolution of symptoms. **Discussion:** HHV-7 infection should be considered in the differential diagnosis of children presenting with fever and neurological involvement of likely viral origin. Although most pediatric cases tend to have favorable clinical outcomes, severe presentations may occur, emphasizing the need for further studies to improve understanding of the optimal approach to these patients.

Keywords: Infection; Human herpesvirus 7; Central nervous system; Child.

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RESUMO

Introdução: O herpesvírus humano tipo 7 (HHV-7) é um vírus comum que geralmente causa infecções autolimitadas em crianças, acometendo raramente o sistema nervoso central. Ainda existem poucas informações na literatura sobre a gravidade das manifestações neurológicas da doença em crianças e sobre seu tratamento. Este trabalho tem por objetivo descrever cinco crianças que apresentaram doença neurológica causada pelo HHV-7 com diferentes formas de manifestação e progressão, discutindo as principais características clínico-epidemiológicas e os cuidados realizados. **Relato de Caso:** Cinco pacientes imunocompetentes, com idades entre dez meses e oito anos, foram diagnosticados com meningoencefalite aguda causada por HHV-7 através de exame de PCR qualitativo realizado no líquido cefalorraquidiano. Sintomas inespecíficos como febre, sintomas gripais, diarreia e vômitos foram observados no início do quadro, seguidos de sintomas neurológicos como irritabilidade, sonolência, convulsões, estrabismo, nistagmos e paralisia de pares cranianos. Nenhum paciente apresentou exantema. Dois pacientes evoluíram com choque ou insuficiência respiratória e foram admitidos no centro de terapia intensiva. Ao todo, 4 pacientes foram tratados com aciclovir venoso e dois pacientes receberam também ceftriaxone. Dois pacientes apresentaram hipóxia cerebral e desenvolveram sequelas da doença e três pacientes receberam alta com resolução dos sintomas. **Discussão:** É importante que se considere a infecção pelo HHV-7 no diagnóstico diferencial de crianças com febre e acometimento neurológico de provável etiologia viral. Embora a maioria das crianças apresente bons desfechos clínicos, casos graves também podem ocorrer, o que reforça a importância de estudos que ampliem o conhecimento sobre a melhor abordagem desses pacientes.

Palavras-chave: Infecção; Herpesvirus humano tipo 7; Sistema nervoso central; Criança.

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Introduction

Acute infections of the central nervous system (CNS) encompass a range of syndromes characterized by the sudden onset of neurological symptoms due to infectious processes involving CNS structures[1]. The clinical presentation can vary depending on the patient's age, the host response to the infection, and the etiology. Signs and symptoms may appear after several days of fever or may have a rapid and fulminant course[2]. Viruses, bacteria, and fungi are common causes of CNS infections, with viruses — including herpesviruses, enteroviruses, arboviruses, coronaviruses, and rabies virus — being the most frequently identified agents[1].

Among the herpesviruses, types 1 and 2 are the most frequently described. Human herpesvirus type 7 (HHV-7) is a rare pathogen, responsible for only 0.3% of all viral infections of the CNS[3,4]. HHV-7 is transmitted via the respiratory route and is considered a ubiquitous virus. Primary infection typically occurs between 18 and 36 months of age, with more than 90% of individuals infected by 5 years old. The presentation is generally asymptomatic, but the infection can also manifest as fever and maculopapular rash, with HHV-7 identified as one of the viruses causing roseola (exanthema subitum)[5,6]. Severe neurological complications from HHV-7 infections can occur rarely, both in immunosuppressed and immunocompetent patients; however, little is known to date about the pathophysiology of CNS involvement. Manifestations of HHV-7 infection in the CNS in children can vary and include meningitis, encephalitis, acute encephalopathy, febrile seizures, acute hemiplegia, facial paralysis, vestibular neuritis.

There are few reports in the literature of CNS infection caused by HHV-7 in pediatric patients. This study aims to describe five cases of neurological disease due to HHV-7 in previously healthy children who were hospitalized from February 2023 to January 2024 at a referral center

for infectious disease treatment in the city of Belo Horizonte, Minas Gerais. The etiological diagnosis of the infection was made through qualitative polymerase chain reaction (PCR) for HHV-7, by testing an expanded viral panel in cerebrospinal fluid (CSF). The viral panel also includes testing for other viruses such as varicella, mumps, herpesviruses types 1 and 2, cytomegalovirus, Epstein-Barr virus, poliovirus, parechovirus, herpesvirus type 6, and parvovirus B19, and is performed by the Central Public Health Laboratory of the State of Minas Gerais at the Ezequiel Dias Foundation (FUNED).

Case Report

Case 1

Male patient, 4 years and 3 months old, admitted to the hospital with meningeal signs, flu-like symptoms, and fever for three days. (Table 1) Cerebrospinal fluid (CSF) was collected, revealing protein = 58mg/dL, glucose = 48mg/dL, and leukocytes = 68 cells/µL (lymphocytes 25%, monocytes 25%, neutrophils 50%), and treatment with ceftriaxone was started due to suspicion of meningoencephalitis. By the second day of treatment, the patient became afebrile and showed good clinical improvement, leading to discontinuation of the antibiotic. On the third day after antibiotic suspension, the patient showed clinical worsening with the onset of prostration, fever, and left facial paralysis. A new CSF analysis showed protein = 53mg/dL, glucose = 39mg/dL, and leukocytes = 105 cells/µL (lymphocytes 60%, monocytes 11%, neutrophils 29%). Due to clinical deterioration, ceftriaxone was reintroduced. The patient presented persistent fever and neurological symptoms for six days, with slow symptom improvement starting from the 7th day of treatment. Brain magnetic resonance imaging (MRI) revealed diffuse cerebral edema, mainly affecting the thalamus, hippocampus, uncus, and anterior commissure. The presence of HHV-7 virus in the CSF was confirmed by qualitative PCR analysis, along with the absence of identification of other viruses by the expanded viral panel. PCR testing was also performed for the bacteria *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, with all results negative, leading to discontinuation of ceftriaxone on the 8th day of treatment. The patient had complete symptom resolution and was discharged fifteen days after admission. Four days after discharge, the child developed paralysis of the left trochlear nerve and was readmitted to the hospital. A computed tomography (CT) scan was performed, showing no abnormalities. New CSF analysis revealed protein = 25mg/dL, glucose = 42mg/dL, and leukocytes = 32 cells/µL (lymphocytes 60%, monocytes 5%, neutrophils 35%). Symptoms resolved spontaneously after 24 hours, and the patient was discharged after 5 days.

Case 2

Male patient, 8 years and 5 months old, admitted to the hospital with a 3-day history of headache, fever, vomiting, and diarrhea, progressing to prostration, nystagmus, and dizziness. (Table 1) On physical examination, the patient showed meningeal signs, and a lumbar puncture was performed revealing cerebrospinal fluid with protein = 10mg/dL, glucose = 52mg/dL, and cells = 74 cells/µL (lymphocytes 58%, monocytes 12%, neutrophils 30%). Brain MRI showed no abnormalities, and electroencephalogram revealed frontotemporal discharges. Intravenous acyclovir was initiated for possible viral meningitis caused by herpesvirus type 1 or type 2, with progressive improvement of symptoms after starting treatment. After 4 days of treatment, real-time PCR (qualitative analysis) for viral detection in the CSF revealed the presence of HHV-7 and absence of other viruses tested by the viral panel. Despite this result, antiviral treatment was continued for 21 days due to clinical improvement. At the end of treatment, the patient was discharged with complete symptom recovery.

Case 3

Male patient, 1 year and 2 months old, presented to the emergency department with a 2-day history of vomiting, high fever, irritability, and drowsiness. (Table 1) On admission, he showed meningeal signs, respiratory distress, cyanosis, salivation, convergent strabismus, and nystagmus. He was admitted to the intensive care unit, where he experienced multiple seizures followed by a cardiorespiratory arrest, responding successfully to resuscitation measures. Ceftriaxone and acyclovir were initiated for possible meningoencephalitis, and a lumbar puncture performed 5 days after treatment initiation showed protein = 66mg/dL, glucose = 120mg/dL, and leukocytes = 2 cells/µL (lymphocytes 100%). Real-time PCR (qualitative analysis) for viral detection in the CSF revealed the presence of HHV-7 and excluded other viruses and bacteria such as *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. Treatment was maintained with ceftriaxone and acyclovir continued for 14 and 21 days, respectively, without symptom improvement. A cranial CT scan showed diffuse supratentorial hypodensity consistent with hypoxic-ischemic syndrome. After 42 days of hospitalization, the patient was discharged with neurological sequelae, presenting spasticity and epilepsy secondary to chronic encephalopathy.

Case 4

A 2-year and 1-month-old male child was admitted to the hospital with suspected meningitis after 6 days of fever, vomiting, drowsiness, strabismus, and facial paralysis. (Table 1) A cranial CT scan showed no abnormalities. Lumbar puncture on admission revealed protein = 13mg/dL, glucose = 52mg/dL, and leukocytes = 11 cells/µL (lymphocytes 97%, neutrophils 3%), and intravenous acyclovir was started for empirical treatment of meningoencephalitis caused by herpesvirus type 1 or 2. After four days of acyclovir, HHV-7 was diagnosed in the CSF by quantitative PCR, and acyclovir was discontinued. The expanded viral panel testing in the CSF excluded the presence of other neurotropic viruses. The patient showed complete symptom resolution and was discharged after eight days of hospitalization.

Case 5

A 10-month-old female patient was admitted to the hospital with a three-day history of diarrhea, associated with generalized tonic-clonic seizures, presenting in shock and respiratory failure (Table 1). Due to suspicion of CNS infection, treatment with intravenous ceftriaxone and acyclovir was initiated. CSF analysis revealed protein = 150mg/dL, glucose = 160mg/dL, and leukocytes = 2 cells/μL (lymphocytes 100%). Real-time PCR for viral detection in the CSF revealed the presence of HHV-7 and excluded other viruses and bacteria such as *N. meningitidis*, *S. pneumoniae*, and *H. influenzae*. As a result, ceftriaxone was discontinued, and acyclovir was maintained for 14 days. At the end of treatment, cranial CT showed diffuse ischemia of the brain parenchyma. Given the persistent poor visual contact and generalized hypotonia, a repeat lumbar puncture was performed, revealing CSF with protein at 33mg/dL, glucose at 95mg/dL, and leukocytes at 3 cells/μL (lymphocytes 12%, monocytes 8%, neutrophils 71%, eosinophils 9%), without detection of new viral agents. The patient was kept on supportive treatment, showing slight symptom improvement, and was discharged after 28 days of hospitalization, maintaining dystonia and spasticity.

Discussion

CNS infection by HHV-7 can occur as a primary infection or due to reactivation of a previous infection, and its clinical spectrum ranges from mild conditions, such as aseptic meningitis, to severe manifestations like encephalitis, encephalopathy, and prolonged seizure episodes. Studies show that, in some cases, the virus can remain latent in neuronal cells after primary infection and reactivate with more severe manifestations, such as CNS disease[7]. The reactivation process has been reported in both immunocompetent and immunosuppressed individuals, and the triggers are not yet well understood[8]. In our study, it was not possible to determine whether the meningitis cases resulted from primary infection or secondary reactivation; however, four out of five patients were under 5 years old, which suggests that the disease may have resulted from primary infection, since most people are exposed to HHV-7 during childhood.

HHV-7 in children has been rarely described as a cause of central nervous system disease. In young children, febrile seizures may be the predominant manifestation, especially in those under two years old. More severe conditions such

Table 1. Clinical, laboratory, and epidemiological aspects of patients with HHV-7 infection in the central nervous system.

	Age	Clinical Manifestations	Cerebrospinal Fluid (CSF)	Diagnosis	Treatment	Outcome
Case 1	4 years and 3 months	flu-like symptoms, fever, facial paralysis, and trochlear nerve paralysis	protein = 58 mg/dL, glucose = 48 mg/dL, and leukocytes = 68 cells/μL (lymphocytes 25%, monocytes 25%, neutrophils 50%)	PCR positive for HHV-7 in cerebrospinal fluid	Ceftriaxone for 8 days	Discharged with symptom resolution
Case 2	8 years and 5 months	headache, fever, vomiting, and diarrhea, progressing to prostration, nystagmus, and dizziness	protein = 10 mg/dL, glucose = 52 mg/dL, and cells = 74 cells/μL (lymphocytes 58%, monocytes 12%, neutrophils 30%)	PCR positive for HHV-7 in cerebrospinal fluid	Acyclovir for 21 days	Discharged with symptom resolution
Case 3	1 year and 2 months	vomiting, fever, irritability, drowsiness, cyanosis, strabismus, nystagmus, and seizures	protein = 66 mg/dL, glucose = 120 mg/dL, and leukocytes = 2 cells/μL (lymphocytes 100%)	PCR positive for HHV-7 in cerebrospinal fluid	Ceftriaxone for 14 days and Acyclovir for 21 days	Discharged with neurological sequelae
Case 4	2 years and 1 month	fever, vomiting, drowsiness, strabismus, and facial paralysis	protein = 13 mg/dL, glucose = 52 mg/dL, and leukocytes = 11 cells/μL (lymphocytes 97%, neutrophils 3%)	PCR positive for HHV-7 in cerebrospinal fluid	Acyclovir for 4 days	Discharged with symptom resolution
Case 5	10 months	diarrhea, seizures, shock, and respiratory failure	protein = 150 mg/dL, glucose = 160 mg/dL, and leukocytes = 2 cells/μL (lymphocytes 100%)	PCR positive for HHV-7 in cerebrospinal fluid	Ceftriaxone for 4 days and Acyclovir for 14 days	Discharged with neurological sequelae

as meningitis and encephalitis are rarer and less frequently reported[8]. A study that evaluated 456 children with viral meningitis over a 7-year period showed an HHV-7 detection rate of only 2.6%[6,8,9]. A systematic review conducted between 1990 and 2022 described the disease in only 26 patients under 16 years old during this period, with a peak incidence at three years of age[6].

The clinical presentation of CNS involvement by HHV-7 can be highly heterogeneous, making it difficult to distinguish from other neurological disorders. The most commonly reported symptoms are fever, headache, vomiting, meningeal signs, and seizures[3,6,8]. Rash, a common manifestation of roseola, is reported in less than 10% of patients with neurological involvement. Some neurological symptoms such as facial paralysis, vestibular neuritis, dysarthria, ataxia, and related ocular symptoms — including optic neuritis, papilledema, and nystagmus — have also been described in less than 10% of infected patients[6,8,10]. In our patients, the initial symptoms were nonspecific and did not allow viral identification; the diagnosis of HHV-7 infection was made only after a positive PCR result from the expanded viral panel performed on cerebrospinal fluid. Most studies describe patients with complete recovery from neurological disease; however, neurological sequelae can also occur, as observed in our work[8]. The literature reports that school-aged children and adolescents may present with more severe neurological symptoms, but the prognosis remains favorable in most cases[6,8,10].

CSF analysis in HHV-7 infections typically demonstrates pleocytosis (30-160 cells/μL) with lymphocyte predominance, normal glucose, and normal or mildly elevated protein levels, as observed in our cases[6,8]. Given the rarity of the infection, it is important to exclude other infectious agents such as bacteria and fungi, as well as structural or metabolic causes[8]. Molecular techniques, especially PCR, can be used to detect HHV-7 DNA in the CSF. The sensitivity and specificity of PCR for HHV-7 in cerebrospinal fluid are not clearly established in the literature, since the infection is still rarely diagnosed and the test is little used in suspected CNS infections[1,8]. Diagnosis is based on a positive test result associated with the presence of suggestive clinical signs, after excluding other infectious causes. Identification of the viral etiology is also considered important for guiding treatment, thus avoiding unnecessary use of antibiotics or antifungals. The literature also reports no characteristic imaging findings of HHV-7 infection in the CNS, but inflammatory lesions, demyelination, and venous thrombosis have been described in some studies[6,8].

The treatment of CNS infection caused by HHV-7 in children is not standardized due to the rarity of cases and the scarcity of controlled studies. Most cases of HHV-7 meningitis in children follow a self-limited course, with complete recovery without specific antiviral therapy, and management is predominantly supportive[8]. Although there is no evidence regarding the therapeutic effect of antiviral therapy in HHV-7 infection, acyclovir, ganciclovir, foscarnet, antibiotics, and corticosteroids have been used in some cases[8]. In our study, two patients did not receive full treatment with acyclovir and achieved complete remission of symptoms, while three patients underwent usual treatment with acyclovir (minimum 14 days), two of whom developed sequelae of the disease. In immunocompromised patients or those with severe manifestations, there are reports of benefit from foscarnet use. Acyclovir, frequently used empirically for viral encephalitis, does not appear to have significant activity against HHV-7[11,12]. Although a recent review showed spontaneous symptom improvement in most patients after 10 days, management should be individualized, with strict clinical support and consideration of antiviral use in severe or refractory cases[8].

A limitation of our study is the small number of cases described in our service. However, considering that central nervous system (CNS) infection by HHV-7 in children is still poorly documented in the literature, we believe these reports contribute significantly to the still limited knowledge about the disease. It is worth noting that there is already a national report of HHV-7 meningoencephalitis in an immunocompetent child, published by Pereira et al. (2023)[13], reinforcing the possibility of severe neurological manifestations even in patients without known immunosuppression. It is important that HHV-7 be included in the differential diagnosis of children with fever associated with neurological symptoms, since the response to commonly used antivirals may not be observed, requiring consideration of other therapeutic options. It is expected that, as PCR tests in the viral panel of cerebrospinal fluid become more widely available, new cases may be identified, reducing current underdiagnosis. While most pediatric cases have favorable outcomes, severe presentations occur, highlighting the need for further research to optimize management strategies

Authors' Contributions

We describe contributions to the papers using the taxanomy (CRediT) provided above: *Conceptualization, Investigation, Methodology, Visualization & Writing – review & editing*: LMO Diniz; DO Russo; MM Moreira. *Project administration, Supervision & Writing – original draft*: LMO Diniz; DO Russo; MM Moreira; BCC Vilela; NA Silva; LLBC Andrade; LB Silva; ALL Jimenez; LLLM Souza; LM Armelin; GSS Santos. *Validation & Software*: BCC Vilela; NA Silva; LLBC Andrade; LB Silva. *Data curation & Formal Analysis*: LMO Diniz.

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