Human Herpes Virus 6 and Encephalitis in Children

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Abstract

Human herpesvirus 6 was the sixth herpesvirus discovered, it is a beta-herpesvirus and is ubiquitous in nature. Primary infection with HHV-6 occurs within the first 2 years of life and is usually associated with an undifferentiated febrile illness, although a subset of children exhibit the classic manifestations of roseola infantum. After primary infection, the virus replicates in salivary glands and is shed in saliva, the recognized route of transmission. It remains latent in lymphocytes and monocytes and persists at low levels in cells and tissues. HHV-6 is probably the most neurotropic virus known, it has been implicated as a cause of encephalitis in transplant recipients but occasionally is reported as a cause of meningitis and encephalitis in immunocompetent individuals. We present the case of a 21-month old infant diagnosed with HHV-6 encephalitis.

Keywords: Human herpesvirus 6, fever, seizure, encephalitis, immunocompetent.

1. Introduction

Human B-lymphotropic virus was first isolated in 1986 from the peripheral blood mononuclear cells (PBMC) of persons with HIV infection or lymphoproliferative disorders. The virus was subsequently determined to have a broad host-cell tropism, including T cells, and the virus was designated "human herpesvirus 6 (HHV-6)." At the time, HHV-6 was the first new human herpesvirus to be discovered in a quarter of a century, and its isolation marked the beginning of an era of discovery in herpesvirology, with the identification of HHV-7 and HHV-8 (Kaposi's sarcoma—associated herpesvirus) during the following decade. HHV-6 was etiologically linked to a human disease in 1988, when Yamanishi et al., described the association of the virus with exanthem subitum (roseola infantum) [32]. HHV-6 was subsequently found to be a ubiquitous agent that infects almost all individuals in early childhood and is capable of becoming reactivated in both normal and immunocompromised persons. HHV-6 is a b-herpesvirus, mostly closely related to HHV-7 and somewhat more distantly related to human cytomegalovirus (CMV).

 Primary infection with HHV-6 occurs within the first 2 years of life and is usually associated with an undifferentiated febrile illness, although a subset of children exhibit the classic manifestations of roseola infantum (exanthem subitum) [5] [3]. The peak age of acquisition of HHV-6 is 6–9 months; the most consistent clinical presentation of infection is abrupt onset of high fever (mean temperature, 39.6°C) [13]. Other common manifestations of infection includ inflammation of tympanic membranes and irritability [24]. Notably, the rash characteristic of roseola is detected either during the illness or following defervescence in ~20% of the patients with primary HHV-6 infection [24]. The mean duration of illness is 6 days, and the most common complication of primary HHV-6 infection is febrile seizures; these occurred in 13% of the children [13].

 After primary infection with HHV-6, the viral genome persists in peripheral blood mononuclear cells (PBMC), possibly in cells of myeloid lineage. The virus also appears to persist in the salivary glands, and viral DNA can be routinely detected in saliva by use of PCR [5]. HHV-6 infects a broad range of cells in vitro, including primary T cells, monocytes, natural killer cells, dendritic cells, astrocytes, and cell lines of T cell, B cell, megakaryocyte, glial, and epithelial origins. CD46 is an essential component of the membrane receptor for HHV-6 [26] , and it functions as a complement regulatory protein present on the surface of all nucleated cells. This is the reason of the broad cell tropism of HHV-6. The principle target cell for HHV-6 is the mature CD4_ Tcell, and the virus has pleiotropic effects on cells of the immune system, which include the ability to disregulate cellular cytokine production, to modulate natural killer cell function, and to modify the expression of key cell surface receptors [20] [21] [9]. In peripheral blood mononuclear cells, viral replication is slow and lytic. The virus is transmitted via oral secretions from adults to infants. In utero transmission has also been suggested, may be transmitted by blood, bone marrow, or transplanted organs [5] [3].

HHV-6 can be cultured from the PBMC of bone marrow transplant (BMT) recipients, but the virus cannot be cultured from the blood of healthy normal adults. Thus, it has been suggested that HH-6 reactivation may contribute to disease in the immunocompromised host; including bone marrow suppression, pneumonitis, encephalitis, and graft versus-host disease in some individuals has been reported [28] [12]. Persons with HIV-1 infection exhibit frequent reactivation of HHV-6, several cases of HHV-6—associated disease in HIV-1—positive persons , including pneumonitis and encephalitis have been described [18]. In most HIV-1—positive adults, HHV-6 reactivation is thought to have a minimal effect on disease progression [8]. In infants with

vertically acquired HIV-1 infection, primary HHV-6 infection has been associated with more rapid progression of disease during the first year of life [17].

2. Case Report

A 21- months - old male, previously healthy, admitted to the University Hospital Center of Tirana for fever without a focus. He had a history of a fourth day fever 39°C. On physical examination appeared relatively well. He was alert, play-full, well-nourished and well orientated, without signs or symptoms of Central Nervous System compromise or Serious Bacterial Infection. The only remarkable sign was a moderate pharynx injection without exudate.

Laboratory investigations on admission revealed a blood cell count WBC 16,200 cells/mm³ (56.1% lymphocytes and 38.6% granulocytes), RBC 4,360,000 cells/mm³, hemoglobin level 11.9 g/dl, hematocrit value 36.5%, platelet count 202,000 cells/mm³, aspartat aminotransferase (AST) 40U/L (nr 0-35U/L), alanin aminotransferase (ALT) 38U/L (nr 0-45U/L), blood urea nitrogen 30mg/dL (nr 10-43mg/dL), creatinin level 0.5mg/dL (nr 0.6-1.4mg/dL), serum total protein level 6.8g/dL (nr 6-8g/dL).

On the second day of hospitalization suddenly the child precipitated in a generalized tonic clonic seizure that lasted 20-25 minutes followed by high fever 40.6°C. The seizure was not controlled with Diazepam therapy via rectum, so continuous therapy with intravenous Phenobarbital was given for 24-hours. Soon after the child entered in a stable state Lumbar puncture was performed. Cerebro-Spinal Fluid (CSF) examination found 5 leukocytes/mm³, glucose level 63mg/dL, total protein level 0.2g/dL. Protein Chain Reaction (PCR) examination identified HHV-6 DNA in CSF, whereas PCRs of CSF for Herpes Simplex Virus (HSV), enteroviruses and bacterial cultures of CSF, blood, urine were all negative.

On the third day of hospitalization, two others generalized seizures of 2-3min duration occurred. Fever subsided on the next day, no rash followed. MRI of the brain performed at the end of the firs week revealed no lesions of white or gray mater. The Electro-encefalogram of the brain was normal too. Phenobarbital was continued orally for 1 month. The child recovered spontaneously without sequelae. Diagnosis at discharge was HHV-6 encephalitis.

3. Discussion

Encephalitis is a rare but severe disease characterized by neurologic dysfunction with central nervous system inflammation. A wide variety of infectious and non-infectious etiologies are associated with encephalitis, though the cause in more than half of cases remains unexplained despite extensive testing. Brain parenchymal inflammation associated with neurologic dysfunction is the strict definition of confirmed encephalitis [30]. Due to the rare cases of pre-mortem brain biopsy specimens available for histopathologic confirmation (particularly in children), clinical correlates are used to direct attention towards probable brain inflammation [31]. In 2013, the International Encephalitis Consortium (IEC) created simplified consensus diagnostic criteria for a standardized case definition of encephalitis and encephalopathy of presumed infectious or autoimmune etiology [10]. Altered mental status for over 24 hours without an alternative cause is required as evidence of neurologic dysfunction, supplemental minor criteria must be present (2 for possible, ≥3 for probable or confirmed): fever ≥38°C within 72 hours, seizures, new focal neurologic findings, cerebrospinal fluid (CSF) pleocytosis (≥5 white blood cells/μL), neuroimaging with brain parenchymal changes or electroencephalogram (EEG) consistent with encephalitis.

In pediatric patients, several factors should be considered when applying the IEC case definition. Simple and complex febrile seizures are a common occurrence in young children and, in isolation, do not necessitate a work-up for encephalitis if the child has returned to baseline mental status. Normal CSF white blood cell counts (WBC) in infants are higher than those cited for adults and a 95th percentile cutoff of ≤19 WBCs/μL for infants ≤1month and ≤9 WBCs/μL for infants 1–2 months are more commonly used to define pleocytosis in these age groups[16]. Young infants are more likely to have infectious encephalitis without pleocytosis, particularly with enterovirus (EV; ~50%) or human parechovirus (HPeV; pleocytosis uncommon) [27] [1] [25]. Therefore, as the IEC criteria suggest, CSF pleocytosis is a supportive, but not necessary criterion for encephalitis, particularly in young infants.

The reported incidence of encephalitis in children in is increased over the past 10 years, which may be partially attributed to increasing use of immunosuppressive therapies and bone marrow and solid organ transplantation associated with an increased risk of encephalitis, as well as improved sensitivity of brain parenchymal imaging using magnetic resonance imaging (MRI) [11] [2]. Prior to this era, the number of encephalitis cases was

decreasing following introduction of vaccines against poliovirus, measles virus, mumps virus, varicella virus, and pertussis [14] [23].

The two main forms of encephalitis are primary infectious encephalitis, resulting from direct invasion of the central nervous system (CNS; most commonly gray matter) by the pathogen, and immune mediated encephalitis, resulting from CNS damage from the immune system (most commonly white matter)[19]. Viruses can invade the CNS via viremia subsequently crossing the blood-brain barrier (arboviruses) or retrograde axonal transport (rabies virus) and infect neurons leading to cytotoxicity (herpes simplex virus; HSV). Additionally, pathogens can cause inflammation leading to tissue damage (West Nile virus; WNV) or cause vasculitis leading to tissue ischemia (varicella zoster virus; VZV), or a combination of these mechanisms [4]. Primarily non-neuroinvasive pathogens infecting non-CNS sites (Mycoplasma pneumoniae, influenza virus respiratory infections), neuroinvasive pathogens infecting the CNS (HSV), tumors (ovarian teratomas), and potentially some vaccinations may trigger CNS autoimmunity due to aberrant immune response against brain antigens. Direct CNS viral infection and triggering of immune mediated disease may co-exist, as illustrated with HSV encephalitis.

An etiology is identified in roughly 50% of cases of encephalitis in children [11] [14]. A broad spectrum of infectious, immune-mediated, rheumatologic, endocrinological, neoplastic, and toxicologic causes all may cause or mimic encephalitis. Infectious causes, including viruses, atypical bacteria, fungi, and parasites are most common, with viruses account for the majority of infectious encephalitis cases in children.

Primary HHV-6 infection has been associated with febrile seizures in infants and young children specially in children 12–15 months of age; in this age group, 36% of children with primary HHV-6 infection had convulsions, versus only 13% of children with non-HHV-6—related febrile illnesses [13]. A parallel PCR-based study found persistence of the virus after primary infection in both PBMC and CSF [6]. In a follow-up prospective study, among children whose first febrile seizures were caused by HHV-6, the incidence of recurrent febrile seizures was significantly less than that among matched controls whose original febrile seizures were due to other causes [15]. Suga et al., found that the frequency of more severe forms of convulsions and postictal paralysis was significantly higher among children with primary HHV-6 infection than it was among those without such infection [29].

HHV-6 has been implicated as a cause of encephalitis in transplantation recipients [28]. The virus has also been implicated as a cause of meningitis and encephalitis in immunocompetent individuals. In a retrospective study of 138 well-studied patients with focal encephalitis of unknown etiology, 9 were found to have HHV-6 DNA in their CSF, whereas the results of PCR and serological assays for other herpesviruses were negative [22]. Clinical outcomes in these cases of HHV-6—associated focal encephalitis were variable, ranging from complete recovery (in 4 cases) to moderate impairment and death (in 1 case) [22].

The point is how frequently HHV-6 DNA can be found in normal brain tissue ; most recently, a survey of 31 normal brain tissues, examined by use of solution PCR, found HHV-6 DNA to be present in approximately one-third of specimens [7]. Taken together, these findings suggest that HHV-6 is, in general, a nonpathogenic, resident virus of the human brain with a potential for neurovirulence. This is supported by in vitro studies demonstrating the ability of HHV-6 to cause a restricted or minimally productive infection of human microglia, astrocytes, and oligodendrocytes.

4. Conclusion

HHV-6 is probably the most neurotropic virus known, it is ubiquitous and infects the vast majority of humans. Primary virus infection in early childhood is frequently accompanied by febrile illness, which may be manifested as classical roseola. HHV-6 has been implicated as a cause of encephalitis in transplant recipients but occasionally is reported as a cause of meningitis and encephalitis in immunocompetent individuals.

5. References

[1] Abzug MJ, Levin MJ, Rotbart HA. Profile of enterovirus disease in the first two weeks of life. The Pediatric infectious disease journal. 1993;12(10):820–824. [PubMed] [Google Scholar]

[2] Bagdure D, Custer JW, Rao S, et al. Hospitalized Children With Encephalitis in the United States: A Pediatric Health Information System Database Study. Pediatric neurology. 2016;61:58–62. [PubMed] [Google Scholar]

[3] Braun DK, Dominguez G, Pellett PE. Human herpesvirus 6, Clin Microbiol Rev, 1997, vol. 10 (pg. 521-67)Google ScholarPubMed

[4] Britton PN, Dale RC, Booy R, Jones CA. Acute encephalitis in children: Progress and priorities from an Australasian perspective. J Paediatr Child Health. 2015;51(2):147–158. [PubMed] [Google Scholar]

[5] Campadelli-Fiume G, Mirandola P, Menotti L. Human herpesvirus 6: an emerging pathogen, Emerg Infect Dis, 1999, vol. 5 (pg. 353-66)Google ScholarCrossrefPubMed

[6] Caserta MT, Hall CB, Schnabel K, et al. Neuroinvasion and persistence of human herpesvirus 6 in children, J Infect Dis, 1994, vol. 170 (pg. 1586-9)Google ScholarCrossrefPubMed

[7] Cuomo L, Trivedi P, Cardillo MR, et al. Human herpesvirus 6 infection in neoplastic and normal brain tissue, J Med Virol, 2001, vol. 63 (pg. 45-51) Google ScholarCrossrefPubMed

[8] Fairfax MR, Schacker T, Cone RW, Collier AC, Corey L. Human herpesvirus 6 DNA in blood cells of human immunodeficiency virusinfected men: correlation of high levels with high CD4 cell counts, J Infect Dis, 1994, vol. 169 (pg. 1342-5) Google ScholarCrossrefPubMed

[9] Flamand L, Stefanescu I, Menezes J. Human herpesvirus-6 enhances natural killer cell cytotoxicity via IL-15, J Clin Invest, 1996, vol. 97 (pg. 1373-81) Google ScholarCrossrefPubMed

[10] Flett KB, Rao S, Dominguez SR, Bernard T, Glode MP. Variability in the Diagnosis of Encephalitis by Pediatric Subspecialists: The Need For a Uniform Definition. J Pediatric Infect Dis Soc. 2013;2(3):267–269. [PubMed] [Google Scholar]

[11] George BP, Schneider EB, Venkatesan A. Encephalitis hospitalization rates and inpatient mortality in the United States, 2000–2010. PloS one. 2014;9(9):e104169. [PMC free article] [PubMed] [Google Scholar]

[12] Griffiths PD, Clark DA, Emery VC. Betaherpesviruses in transplant recipients, J Antimicrob Chemother, 2000, vol. 45 (pg. 29-34) Google ScholarCrossrefPubMed

[13] 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, vol. 331 (pg. 432-8) Google ScholarCrossrefPubMed

[14] Iro MA, Sadarangani M, Goldacre R, Nickless A, Pollard AJ, Goldacre MJ. 30- year trends in admission rates for encephalitis in children in England and effect of improved diagnostics and measles-mumps-rubella vaccination: a population-based observational study. The Lancet Infectious diseases. 2017 [PubMed] [Google Scholar]

[15] Jee SH, Long CE, Schnabel KC, et al. Risk of recurrent seizures after a primary human herpesvirus 6—induced febrile seizure, Pediatr Infect Dis J, 1998, vol. 17 (pg. 43-8) Google ScholarCrossrefPubMed

[16] Kestenbaum LA, Ebberson J, Zorc JJ, Hodinka RL, Shah SS. Defining cerebrospinal fluid white blood cell count reference values in neonates and young infants. Pediatrics. 2010;125(2):257–264. [PMC free article] [PubMed] [Google Scholar]

[17] Kositanont U, Wasi C, Wanprapar N, et al. Primary infection of human herpesvirus 6 in children with vertical infection of human immunodeficiency virus type 1, J Infect Dis, 1999, vol. 180 (pg. 50-5) Google ScholarCrossrefPubMed

[18] Knox KK, Carrigan DR. Disseminated active HHV-6 infections in patients with AIDS, Lancet, 1994, vol. 343 (pg. 577-8) Google ScholarCrossrefPubMed

[19] Lewis P, Glaser CA. Encephalitis. Pediatrics in review / American Academy of Pediatrics. 2005;26(10):353–363. [PubMed] [Google Scholar]

[20] Lusso P, Malnati M, De Maria A, et al. Productive infection of CD4+ and CD8+ mature human T cell populations and clones by human herpesvirus 6: transcriptional down-regulation of CD3, J Immunol, 1991, vol. 147 (pg. 685-91) Google ScholarPubMed

[21] *Lusso P, De Maria A, Malnati M, et al. Induction of CD4 and susceptibility to HIV-1 infection in human CD8+ T lymphocytes by human herpesvirus 6, Nature, 1991, vol. 349 (pg. 533-5) Google ScholarCrossrefPubMed*

[22] *McCullers JA, Lakeman FD, Whitley RJ. Human herpesvirus 6 is associated with focal encephalitis., Clin Infect Dis, 1995, vol. 21 (pg. 571-6) Google ScholarCrossrefPubMed*

[23] *Pahud BA, Glaser CA, Dekker CL, Arvin AM, Schmid DS. Varicella zoster disease of the central nervous system: epidemiological, clinical, and laboratory features 10 years after the introduction of the varicella vaccine. The Journal of infectious diseases. 2011;203(3):316–323. [PMC free article] [PubMed] [Google Scholar]*

[24] *Pruksananonda P, Hall CB, Insel RA, et al. Primary human herpesvirus 6 infection in young children, N Engl J Med, 1992, vol. 326 (pg. 1445-50) Google ScholarCrossrefPubMed*

[25] *Renaud C, Harrison CJ. Human Parechovirus 3: The Most Common Viral Cause of Meningoencephalitis in Young Infants. Infect Dis Clin North Am. 2015;29(3):415–428. [PubMed] [Google Scholar]*

[26] *Santoro F, Kennedy PE, Locatelli G, et al. CD46 is a cellular receptor for human herpesvirus 6, Cell, 1999, vol. 99 (pg. 817-27) Google ScholarCrossrefPubMed*

[27] *Seiden JA, Zorc JJ, Hodinka RL, Shah SS. Lack of cerebrospinal fluid pleocytosis in young infants with enterovirus infections of the central nervous system. Pediatr Emerg Care. 2010;26(2):77–81. [PubMed] [Google Scholar]*

[28] Singh N, Paterson DL. Encephalitis caused by human herpesvirus-6 in transplant recipients: relevance of a novel neurotropic virus, Transplantation, 2000, vol. 69 (pg. 2474-9) Google ScholarCrossrefPubMed

[29] 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, vol. 33 (pg. 597-603) Google ScholarCrossrefPubMed

[30] 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(3):303–327. [PubMed] [Google Scholar]

[31] Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis. 2013;57(8):1114–1128. [PMC free article] [PubMed] [Google Scholar]

[32] Yamanishi K, Okuno T, Shiraki K, et al. Identification of human herpesvirus-6 as a causal agent for exanthem subitum, Lancet, 1988, vol. 1 (pg. 1065-7) Google ScholarCrossrefPubMed