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Clinical Observations

# Fatal Human Herpesvirus 6–Associated Encephalitis in Two Boys With Underlying *POLG* Mitochondrial Disorders

**Duha Al-Zubeidi MD [a], Mathula Thangarajh MD, PhD [b], Sheel Pathak MD [c], Chunyu Cai MD, PhD [d], Bradley L. Schlaggar MD, PhD [c], Gregory A. Storch MD [e], Dorothy K. Grange MD [f], Michael E. Watson Jr. MD, PhD [g,*]**

[a] *Division of Pediatric Infectious Diseases, Department of Pediatrics, Children's Mercy Hospital, Kansas City, Missouri*
[b] *Division of Epilepsy, Neurophysiology, and Critical Care Neurology, Department of Neurology, Children's National Medical Center, Washington, DC*
[c] *Department of Neurology, Washington University, St. Louis, Missouri*
[d] *Department of Pathology and Immunology, Washington University, St. Louis, Missouri*
[e] *Division of Pediatric Infectious Diseases, Department of Pediatrics, Washington University, St. Louis, Missouri*
[f] *Division of Genetics and Genomic Medicine, Department of Pediatrics, Washington University, St. Louis, Missouri*
[g] *Division of Pediatric Infectious Diseases, Department of Pediatrics, University of Michigan, Ann Arbor, Michigan*

ABSTRACT

**BACKGROUND:** Human herpesvirus 6 is a significant cause of the febrile illness roseola infantum in young children. Infection with human herpesvirus 6 typically causes a self-limited febrile illness but occasionally is associated with central nervous system manifestations, including febrile seizures and encephalitis. Host factors associated with severe manifestations of human herpesvirus 6–associated neurological disease remain poorly characterized. **CASE REPORTS:** We report two previously healthy young boys with human herpesvirus 6–associated encephalitis who developed a progressive, and ultimately fatal, encephalopathy with refractory movement disorder concurrent with acquisition of acute human herpesvirus 6 infection. Both children were treated with the antiviral ganciclovir without improvement of their neurological symptoms, although quantitative human herpesvirus 6 polymerase chain reaction of cerebrospinal fluid and/or blood confirmed a decline in viral load with treatment. The clinical course in both cases was most consistent with Alpers-Huttenlocher syndrome, given the intractable seizures, developmental regression, and, ultimately, death due to liver and renal failure. In support of this, postmortem analysis identified both children to be compound heterozygous for mutations in the mitochondrial polymerase γ gene, *POLG*. **CONCLUSIONS:** *POLG* mutations are associated with Alpers-Huttenlocher syndrome; however, no prior studies have examined the role of acute human herpesvirus 6 infection in these patients presenting with severe neurological disease. It is possible the *POLG* mutation phenotype was unmasked and/or exacerbated by human herpesvirus 6 infection in these two patients, potentially contributing to a more rapid clinical deterioration. This report provides new insight into a previously unrecognized association between *POLG* mutations and poor neurological outcome after human herpesvirus 6 infection.

***Keywords:*** human herpesvirus 6 (HHV-6), *POLG*, encephalitis, child

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## Introduction

Human herpesvirus 6 is the primary cause of a common illness of infants and young children, roseola infantum, also known as "the sixth exanthematous disease of childhood" or "3-day fever".[1] Primary infection with human herpesvirus 6 occurs during childhood, usually between 6 and 14 months of age, and affects most people by 24 years of age.[2] Human

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* Communications should be addressed to: Dr. Watson; University of Michigan Medical School; 1150 West Medical Center Dr; MSRB3; Room 8301, SPC 5646; Ann Arbor, Michigan 48109-5684.
*E-mail address:* mikeannaw@gmail.com

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herpesvirus 6 infection may be asymptomatic, and disease is typically a self-limiting febrile illness often associated with a rash (exanthema subitum). Rarely, human herpesvirus 6 can be associated with pneumonitis, hepatitis, and central nervous system (CNS) manifestations.[3] Human herpesvirus 6 is a neurotropic virus that has been associated with a variety of neurological disorders, including febrile seizures, encephalitis, mesial temporal lobe epilepsy, and multiple sclerosis.[3,4] Distinct from the other human herpesviruses, human herpesvirus 6 undergoes chromosomal integration within leukocytes to establish a latent and lifelong infection that may reactivate with immunosuppression.[1,2] Two subgroups of human herpesvirus 6, variants A and B, are distinguishable by their genetic, biologic, and epidemiologic characteristics. Human herpesvirus 6B causes almost all primary infections in infants and is the predominant variant associated with reactivation in older immunocompetent and immunocompromised individuals. Human herpesvirus 6A is a relatively less common cause of illness, except within the African continent, but may be more likely associated with certain conditions, including multiple sclerosis and rhombencephalitis.[5,6]

Because of overlapping features, it can sometimes be difficult to determine the etiology of CNS disorders and distinguish among infectious agents, metabolic disorders, or genetic conditions. Mutations in the human *POLG* gene, encoding the mitochondrial DNA polymerase γ protein, have recently been identified in a number of neurological syndromes including encephalopathy, seizures, chronic progressive external ophthalmoplegia, adult-onset cerebellar ataxia, and Alpers-Huttenlocher syndrome.[7-12] In spite of some overlapping features, an association between human herpesvirus 6–associated CNS disease and mitochondrial disorders has not been previously documented. In this report, we describe two cases of previously healthy young boys diagnosed with human herpesvirus 6 encephalitis with refractory seizures who developed a progressive and fatal encephalopathy, both of whom were later identified as having underlying mutations in *POLG*. We review the literature with the goal of highlighting a previously unrecognized and potentially significant association between mitochondrial disorders and poor neurological outcomes after human herpesvirus 6 infection.

## Patient Descriptions

### *Patient A*

A previously healthy 10-month-old boy presented with status epilepticus and a declining level of consciousness. There was no preceding illness or fever. His birth and medical histories were noncontributory, and his developmental milestones were appropriate for age. His immunizations were up to date. The family history was unremarkable. Electroencephalography (EEG) revealed diffuse slowing and absence of normal sleep-wake architecture, with no significant interictal discharges and no electrographic seizures evident. Both cranial computed tomography scan and magnetic resonance imaging results were normal. Physical examination revealed a diminished attentiveness to external stimuli. Cranial nerve examination was significant for hippus pupils and lack of optokinetic nystagmus and near-constant, low-frequency myoclonic eye movements. Motor examination revealed distal extremity chorea and similar low-frequency myoclonic movements in the right upper extremity and right side of the abdomen. He was treated with antiepileptic drugs for presumptive status epilepticus, ultimately requiring a propofol infusion. During his hospital admission, he had multiple investigations with EEG for these movements, which did not have a clear EEG correlate for a large part of his admission. Later in his admission, the movements became more pronounced and diffuse and were associated with EEG changes, bringing up the question as to whether his earlier EEG was not picking up discharges that may have been more deeply generated and that he actually was having seizures.

Routine hematological and biochemical study results, including serum ammonia, ceruloplasmin, serum amino acids, and urine organic acids, were normal. Cerebrospinal fluid (CSF) was clear with 1 nucleated cell per $mm^3$, protein of 83 mg/dL, and glucose of 68 mg/dL. Paraneoplastic antibody test results, including anti-n-methyl-D-aspartate (NMDA) receptor antibody testing in both serum and CSF, were negative. Results of an extensive investigation for infectious agents were positive only for human herpesvirus 6B in the plasma and CSF at admission and again at 1, 2, and 3 weeks. Quantitative plasma human herpesvirus 6 polymerase chain reaction (PCR) result was 11,300 copies/mL on admission and was positive at less than the accurate level of detection (<1000 copies/mL) in the subsequent weeks (ARUP Laboratories, Salt Lake City, UT). Quantitative CSF human herpesvirus 6 PCR result was positive at <1000 copies/mL throughout his hospitalization. He received two doses of intravenous (IV) immunoglobulin (2 g/kg) with no improvement and subsequently was treated with ganciclovir (5 mg/kg/dose IV every 12 h).

He was diagnosed with a hyperkinetic movement disorder characterized by chorea, myoclonus, and encephalopathy, presumably secondary to his recent human herpesvirus 6 infection. In spite of treatment with 21 days of ganciclovir, the myoclonus and chorea persisted. Approximately 8 weeks after his initial admission, he developed liver and renal failure with anasarca in addition to intractable myoclonic movements of the face and the trunk. The family elected to redirect care and the patient died. Genetic testing for mitochondrial disorders was performed and was positive for *POLG* mutations with the presence of two heterozygous mutations: c.1120C>T (p.Arg374X) and c.1399G>A (p.Ala467Thr) in exons 12 and 17, respectively. Both mutations have been previously reported in individuals with progressive external ophthalmoplegia.[13]

Postmortem examination revealed CNS and liver findings characteristic of Alpers-Huttenlocher syndrome.[11,12] The brain was developmentally normally formed but showed mildly dilated ventricular system (Figure A) and patchy, ill-defined, white discolorations throughout the superficial cortical gray matter that blurred the gray-white junction (Figure A asterisks). These areas did not conform to vascular territory and were more prominent in the striate cortex of the occipital lobes. Microscopically, the white patches were areas of marked neuronal loss and gliosis (Figure B). A significant component of Alzheimer type II astrocytes were present throughout but most prevalent in the thalamus (Figure C). Vacuolated changes were also present and were most prominent in the dentate nuclei of the cerebellum (Figure D). The hippocampi showed marked loss of neurons and gliosis in Sommer's sector. There were no significant microglia nodules, intraneuronal inclusions, lymphoplasmacytic infiltrate, or focal destructive lesions to suggest ongoing viral encephalitis. Gross and microscopic examination of the liver revealed ongoing micronodular cirrhosis and marked cholestasis, characterized by presence of bridging and pericellular fibrosis (Figure E), bile ductular proliferation, (Figure F) and frequent bile plugs (Figure F arrows).

### *Patient B*

A previously healthy 12-month-old boy presented with new-onset focal myoclonic status epilepticus requiring pentobarbital coma and hypothermia for control. Physical examination on admission was consistent with pentobarbital coma. As sedation was weaned, the patient demonstrated signs of subtle right hemiparesis. EEG at admission revealed status epilepticus with seizures involving the right arm and leg that corresponded to left central rhythmic discharges. Cranial magnetic resonance imaging revealed mild diffusion restriction in the high left frontal lobe involving the precentral and postcentral gyri, presumably secondary to prolonged seizures. Routine hematological and biochemical study results including serum ammonia, ceruloplasmin, and urine