



Clinical Observations

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



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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

Pediatr Neurol 2014; 51: 448–452

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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

Article History:

Received December 19, 2013; Accepted in final form April 5, 2014

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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 mm³, 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

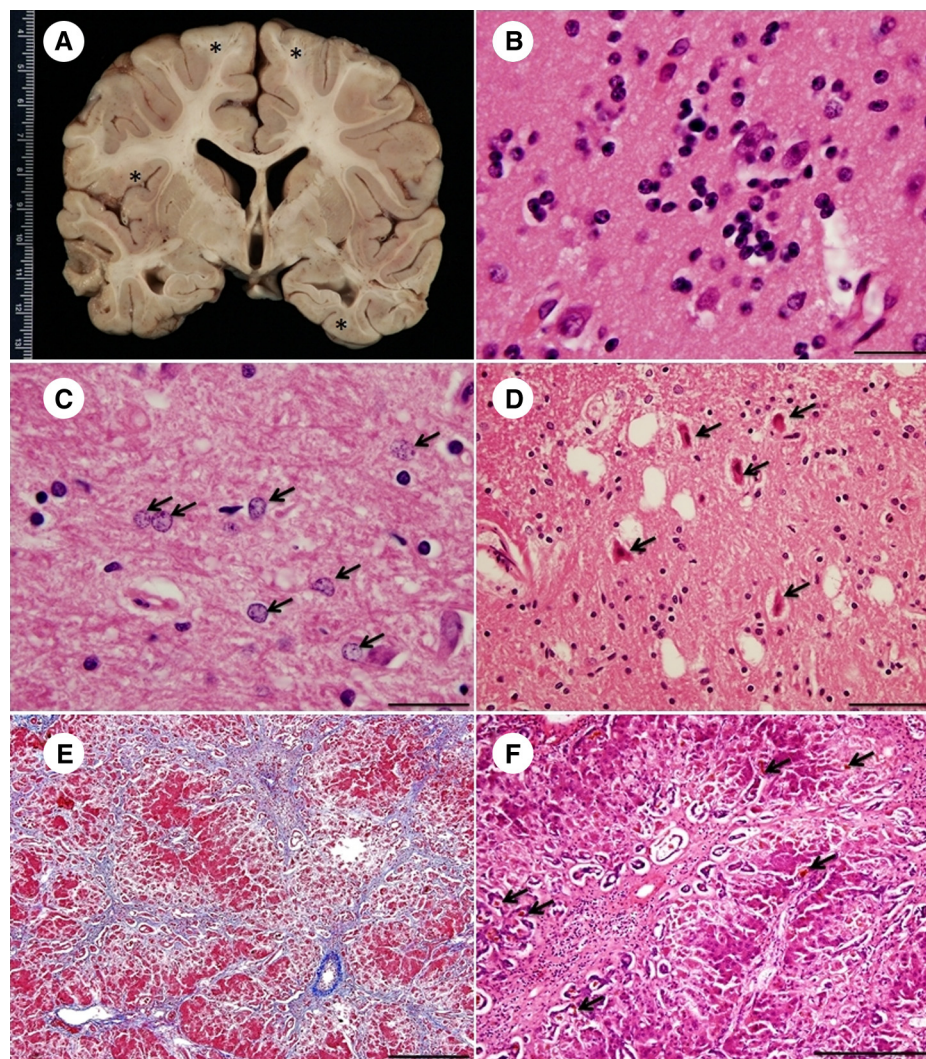


FIGURE.

Autopsy findings of brain and liver for Patient A. (A) Coronal section of the brain at the basal ganglia level shows dilated ventricular system and multiple patches of white discoloration in the superficial cortex (asterisks). (B) Microscopically, the white patches are composed of gliosis and neuronal loss. (C) The thalamus shows frequent Alzheimer type II astrocytes (arrows). (D) Cerebellar dentate nucleus showed prominent vacuolated changes. The remaining neurons (arrows) showed intensely eosinophilic cytoplasm and pyknotic nuclei. (E) Trichrome-stained section from the liver highlighted bridging and pericellular fibrosis. (F) Hematoxylin and eosin–stained section from the liver showed marked ductular proliferation and frequent bile plugs (arrows). (Scale bars: B and C 20 μ m, D 50 μ m, E 200 μ m, and F 100 μ m.) (Color version of the figure is available in the online edition.)

organic acids were normal. CSF analysis revealed 1 nucleated cell per mm^3 , protein of 40 mg/dL, and glucose of 66 mg/dL. Both serum and CSF test results for anti-NMDA receptor antibodies and a paraneoplastic antibody panel were negative. Extensive evaluation for bacterial and viral etiologies identified only human herpesvirus 6B with positive plasma and CSF PCR analyses at admission and 1 week later.

He was diagnosed with human herpesvirus 6 encephalitis with new-onset epilepsy and was treated with 21 days of ganciclovir (5 mg/kg/dose IV every 12 h) and antiepileptic drugs. Over the next few months, he developed myoclonic seizures involving the right neck and upper arm. He was treated with additional antiepileptic drugs, and later a ketogenic diet was attempted with partial abatement of his seizures. Repeat evaluation for human herpesvirus 6 viral infection revealed CSF and plasma human herpesvirus 6 PCR results were negative; whole-blood human herpesvirus 6 PCR result was positive, presumably due to chromosomal integration within leukocytes. His human herpesvirus 6 immunoglobulin M and immunoglobulin G titers were 1:20 and 1:40, respectively, at admission and 1:20 and 1:320, respectively, 6 weeks later. At approximately 22 months of age he was readmitted with liver and renal failure and anasarca. The clinical scenario of progressive liver failure and

intractable seizures prompted a genetic evaluation for a mitochondrial disorder, which identified *POLG* mutations. The family elected to redirect care and the patient died. *POLG* sequence analysis confirmed the presence of two heterozygous mutations: c.2243G>C and c.2740A>C on exons 12 and 17, respectively. Both mutations have been previously reported in individuals with Alpers-Huttenlocher syndrome or ataxic neuropathy (Online Mendelian Inheritance in Man (www.OMIM.org) OMIM 174763.0013) and with liver disease, encephalopathy, and myopathy.^{11,13}

Discussion

We report two children who illustrate a previously unrecognized presentation of an underlying mitochondrial disorder triggered by severe human herpesvirus 6 CNS infection. Both boys were previously healthy and presented with progressive encephalopathy, seizures, and hyperkinetic movement disorders with evidence of active CNS

human herpesvirus 6B infection. Neurological symptoms did not cease following initiation of antiviral medication. Neither boy was initially suspected of having a mitochondrial disorder. However, ultimately, both boys developed progressive liver and renal failure contributing to their demise. Their clinical courses were atypical for human herpesvirus 6—associated infection and are the first cases in the literature that describe this association.

Few reports adequately document severe neurological manifestations of human herpesvirus 6 infection in immunocompetent children. One report described a 14-month-old girl who presented with febrile status epilepticus with chorea and developmental regression.¹⁴ Her laboratory evaluation revealed human herpesvirus 6 infection; variants A and B were both detected in the CSF. She was treated with IV immunoglobulin and foscarnet with improvement except for residual hypotonia, poor coordination, complete absence of expressive language, and developmental delay.¹⁴ The few cases reported do not suggest a specific underlying reason for the severe human herpesvirus 6 infection with development of residual neurological complications, such as the finding of an underlying genetic disorder.^{3,4,6,14,15}

POLG encodes the mitochondrial DNA polymerase γ and is essential for replication and repair of mitochondrial DNA.⁹ Mutations in *POLG* account for one of the most common causes of mitochondrial disease in both children and adults.^{9,13} Deficiency of *POLG* results in mitochondrial DNA depletion and deletions. There is a broad spectrum of associated clinical phenotypes in *POLG*-related mitochondrial disease, including Alpers-Huttenlocher syndrome, childhood myocerebrohepatopathy spectrum, myoclonic epilepsy myopathy sensory ataxia, ataxia neuropathy spectrum, autosomal recessive progressive external ophthalmoplegia, and chronic progressive external ophthalmoplegia.^{7–11,13,16} There is variable age of onset, from infancy to adulthood, and multiple tissues may be affected. Most of the conditions are autosomal recessive, usually associated with compound heterozygosity for two different *POLG* mutations. However, autosomal dominant inheritance is also observed, especially in chronic progressive external ophthalmoplegia.⁸ Alpers-Huttenlocher syndrome is characterized by the triad of refractory seizures, episodic psychomotor regression that is triggered by intercurrent infection, and hepatopathy with or without acute liver failure.^{11,12}

In the case studies presented here, two previously healthy children experienced severe neurological manifestations during human herpesvirus 6 infection and were found to have an underlying *POLG*-related mitochondrial disorder. The clinical course in both cases is most consistent with Alpers-Huttenlocher syndrome, given the intractable seizures, developmental regression, and, ultimately, death due to liver and renal failure. The diagnosis of a *POLG*-related disorder was made by genetic testing several weeks to months after their initial presentations with an human herpesvirus 6 infection. Progression of symptoms and deterioration of mitochondrial disorders in association with an intercurrent illness have been well described.¹⁷ However, we are not aware of prior reports of severe human herpesvirus 6 encephalitis in individuals with *POLG* mutations or other mitochondrial disorders. It is not clear whether the underlying deficiency of polymerase γ activity

makes these individuals more susceptible to human herpesvirus 6 infection, specifically in the brain, and if so, what the mechanism might be.

Some antiviral drugs can inhibit *POLG* activity, leading to mitochondrial dysfunction.¹⁸ This finding has been described primarily in patients with human immunodeficiency virus infection who are treated long term with the thymidine analog azidothymidine and other antiviral agents.^{18,19} Ganciclovir, a guanosine analog, may similarly induce mitochondrial DNA damage after its initial phosphorylation by the activity of a herpesvirus viral thymidine kinase, particularly that of herpes simplex virus.²⁰ The human herpesvirus 6 kinase U69 has been demonstrated to have only modest activity with ganciclovir compared with other herpesvirus kinases, and, although plausible, the potential for mitochondrial damage from ganciclovir use in the setting of human herpesvirus 6 infection has not been ascertained.²¹ Both of the boys described in this report initially presented with seizures and neurological symptoms associated with human herpesvirus 6 infection, before receiving any treatment. However, given the potential for antiviral-induced mitochondrial injury we cannot exclude the possibility that the ganciclovir treatment they received during the course of the illness could have had a detrimental impact on their residual *POLG* activity and may have hastened progression of their multiorgan system disease. This possibility may necessitate careful consideration of risks and benefits in the future use of antiviral medications in patients with suspected mitochondrial disorders.

In conclusion, identifying children with *POLG* mutations can be challenging. *POLG*-related mitochondrial disorders should be suspected in children presenting with status epilepticus or epilepsy partialis continua with severe human herpesvirus 6 infection refractory to antiviral or antiepileptic therapy. In our cases the disease outcome was poor, and both of our patients died within a year of initial presentation. The presence of a mitochondrial disorder makes our cases unique among other reported cases of severe human herpesvirus 6—associated conditions. This association may be coincidental because human herpesvirus 6 is a common infection in this age group, and patients with underlying mitochondrial disease are at risk for decompensation during viral illnesses. However, this particular association could be significant. It may be worth exploring testing for *POLG* by DNA sequencing, and possibly evaluation for other mitochondrial disorders, in children presenting with severe human herpesvirus 6 infections presenting as prolonged encephalitis.

The authors thank the faculty and staff of the Washington University Division of Pediatric Infectious Diseases, the Department of Neurology, the Department of Genomic Medicine, and the St. Louis Children's Hospital Virology Laboratory for their assistance.

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