

# Intracranial Hemorrhage in Herpes Simplex Encephalitis: An Unusual Presentation

Guliz Erdem, MD\*,  
Paula A. Vanderford, MD<sup>†</sup>, and  
Robert D. Bart, Jr, MD<sup>\*‡</sup>

We describe a 14-month-old patient with atypical presentation of herpes simplex encephalitis. She initially presented with fever, lethargy, seizures, and large hemorrhages in the right parietal lobe, and clinical findings suggestive of a hypercoagulable state. The etiology of coagulation abnormality was not identified, although it was suggested as a possible causative factor in severe bleeding along with acute neuronal lysis as a result of infection. Although large intracerebral hemorrhages are occasionally described with systemic herpes infection, this presentation is unusual beyond the infant period. © 2002 by Elsevier Science Inc. All rights reserved.

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## Introduction

Herpes simplex virus (herpesvirus) is the most frequent agent causing sporadic viral encephalitis [1]. Typically, herpesvirus produces hemorrhagic necrotizing encephalitis in the medial temporal and frontal lobes [2]. A 14-month-old infant who presented with bilateral large hemorrhages in the right parietal lobe and clinical findings suggestive of a hypercoagulable state is described in this study. The diagnosis of herpes simplex encephalitis was

confirmed late in the hospital course with a positive herpesvirus polymerase chain reaction. Large areas of hemorrhage in herpes simplex encephalitis are reported in infants with disseminated herpesvirus infection and infrequently in adults, although hemorrhage has not been previously described in other pediatric patients [3,4].

## Case Report

A 14-month-old female was admitted to the Kapiolani Medical Center, Honolulu, Hawaii, with generalized seizures. She had developed fever and irritability 4 days before admission, which was followed by drooling, decreased oral intake, lethargy, and generalized seizures. A computed tomography scan of her head performed in an outlying hospital revealed a large hemorrhage in the right parietal parenchyma with surrounding edema, three smaller lesions with surrounding edema in the same area, and similar smaller symmetric lesions on the left side. There was no midline shift or meningeal enhancement. She had no history of trauma or ill contacts and no previous history of bleeding. Her past medical history was significant with premature delivery at 29 weeks of gestation to a 17-year-old mother with no history of complications. The infant had intermittent apneas and bradycardias during the first week of life. She had several head ultrasound studies, which were reported to be normal. She was able to walk and say a few words before her illness. She was in foster care for social reasons.

At the time of her admission she was lethargic. Her weight was 11 kg (ninety-fifth percentile corrected for gestation). The deep tendon reflexes were decreased in the lower extremities. She had no focal neurologic findings. The results of the remainder of her physical examinations were within normal limits. The initial biochemistry and coagulation studies could not be performed because several blood samples obtained from arterial and venous lines clotted. After several attempts the coagulation studies including prothrombin time (11.6 seconds, normal = 10.5-12.5 seconds), partial thromboplastin time (33 seconds, normal = 27-35 seconds), fibrinogen (234 mg/dL, normal = 200-400 mg/dL), antithrombin III (103%, normal = 85%-122%), protein C (94%, normal = 60%-138%), protein S levels (53%, normal  $\geq$  60%, the result considered to be not significantly low) were obtained. However, fresh-frozen plasma was administered empirically while waiting for the protein C and protein S levels, because she appeared to have a hypercoagulable state. Several laboratory tests were performed to find the etiology of intracranial hemorrhage, testing for causes such as infections, blood disorders, cardiac disorders, trauma, vasculitis, and several metabolic diseases. Her complete blood count, electrolytes, and transaminases were at normal levels. Her reticulocyte count was normal, and sickle test was negative. Her arterial blood gas measurements did not reveal acidosis. Anticardiolipin antibodies and coagulation factor II and factor V mutations were absent. She was noted to be heterozygous for 5,10-methylenetetrahydrofolate reductase. Results of influenza, *Cytomegalovirus*, echovirus, Coxsackie, varicella virus, and mycoplasma serologies were negative. Her neuroimaging findings were not reported to be consistent with vasculitis. An echocardiogram result was normal. Her lumbar puncture at the time of admission revealed 700/ $\mu$ L red blood cells and 33/ $\mu$ L white blood cells with lymphocyte predominance. The cerebrospinal fluid protein and

From the \*Department of Pediatrics, the <sup>†</sup>Division of Pediatric Intensive Care, and the <sup>‡</sup>Department of Internal Medicine; University of Hawaii John A. Burns School of Medicine; Honolulu, Hawaii.

Communications should be addressed to:  
Dr. Bart; Professor of Pediatrics and Internal Medicine; Division Chief, Neurology; University of Hawaii John A. Burns School of Medicine; Kapiolani Medical Center for Women and Children; 1319 Punahou Street, Suite 999; Honolulu, HI 96826.  
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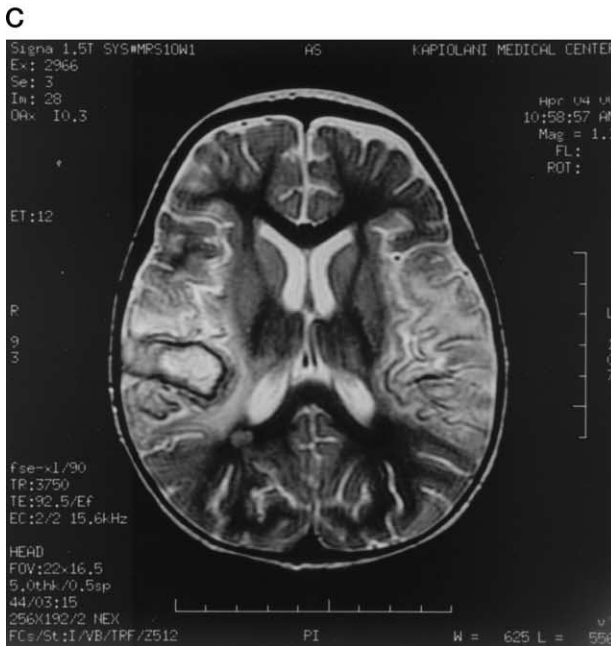
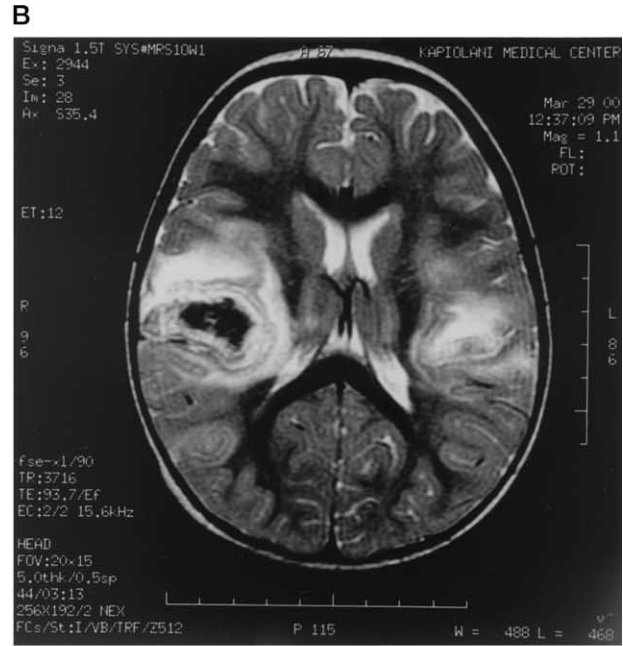
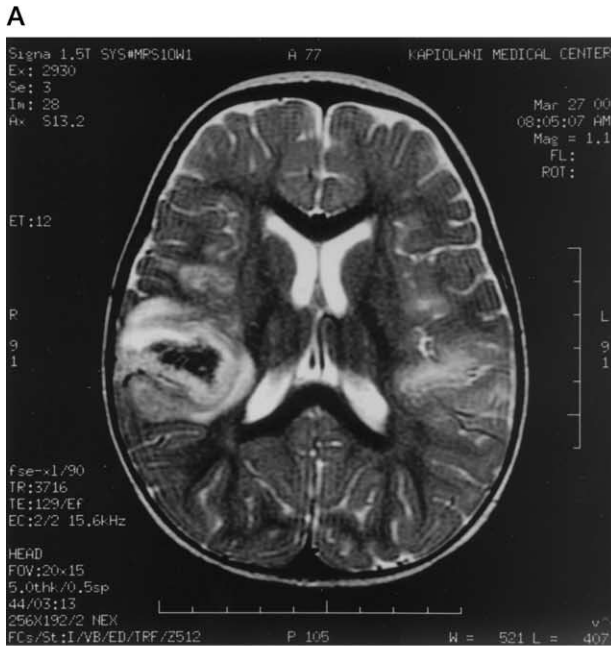


Figure 1. (A) Initial  $T_2$ -weighted axial image reveals heterogenous hemorrhage in the right temporal lobe and bilateral temporal edema (TR = 3,716, TE = 129). (B) Follow-up scan reveals the right-sided hemorrhage and progressive edema on  $T_2$ -weighted image (TR = 3,716, TE = 93.7). (C) Decreasing edema and hemorrhage and frontal atrophy on  $T_2$ -weighted image is indicated (TR = 3,750, TE = 92.5).

glucose were 38 mg/dL and 60 mg/dL, respectively. She was empirically begun on intravenous acyclovir (20 mg/kg/dose every 8 hours).

On her second hospitalization day, she became comatose. She continued to have occasional seizures despite fosphenytoin and subsequently phenobarbital. Her cranial magnetic resonance imaging on the second day of hospitalization revealed a large right temporoparietal hemorrhage with surrounding edema and additional symmetric areas of edema involving both temporoparietal lobes and both posterior frontal lobes, thalami, and insular regions (Fig 1A). Magnetic resonance angiography for both cerebral arteries and veins were normal.

She continued to have fevers up to 103°F for 3 days. A repeat magnetic resonance imaging on the third day of hospitalization revealed evolving hemorrhage with increasing edema of both temporoparietal lobes, parasagittal area, thalami, and bilateral insular regions, as well as increasing areas of  $T_1$  signal along the gyral surfaces (Fig 1B). She developed hepatosplenomegaly along with elevated liver enzymes during the first week of hospitalization. She continued to receive intravenous acyclovir. The herpesvirus polymerase chain reaction was reported as positive. Her

cerebrospinal fluid and blood viral cultures remained negative. She received 21 days of acyclovir treatment with improvement in magnetic resonance imaging findings beginning from the eighth day of treatment with resolving hemorrhages and subsiding bilateral temporoparietal edema (Fig 1C). A repeat herpesvirus polymerase chain reaction, which was performed after 7 days of acyclovir treatment, was negative. Her level of consciousness improved, and she was successfully extubated after 10 days. She continued to have severe bulbar dysfunction but no seizures on antiepileptic drugs at the time of her discharge from the hospital. She has continued to be a spastic quadriparetic child but was feeding by mouth 9 months after her discharge.

## Discussion

Herpesvirus is the most common identifiable cause of encephalitis in the United States [5]. Herpes simplex encephalitis is well recognized in adolescents and adults,

and a high index of suspicion is usually present in patients presenting with acute onset of encephalopathy, focal seizures, and neurologic deficits. The cerebrospinal fluid findings, including the presence of erythrocytes and lymphocytes and especially the presence of focal temporal or frontal abnormalities on magnetic resonance imaging scans, also supported the decision to treat with intravenous acyclovir [6]. There are few clinical descriptions of herpes simplex encephalitis except in the infant and adolescent periods in the pediatric literature. Our patient was admitted for evaluation of acute onset of seizures. She had fevers and cerebrospinal fluid pleocytosis suggestive of an infectious process. However, her clinical presentation with seizures, unilateral parietal hemorrhage, bilateral parietal edema, and recurrent clotting of arterial blood samples during the first hours of her hospitalization seemed more consistent with a hypercoagulable state that was induced by an infectious agent.

Vascular changes that have been reported in herpes simplex encephalitis include areas of hemorrhagic necrosis and perivascular cuffing [1]. Although petechial hemorrhages and smaller lesions have been described in herpes simplex encephalitis, large areas of hemorrhage and edema, as described in our patient, are unusual and may delay the diagnosis and treatment [3,4]. It may be argued that the magnetic resonance imaging abnormalities observed in this patient are in the distribution of middle cerebral arteries and they may represent bilateral infarctions with hemorrhage. However; infarction with hemorrhagic transformation is unlikely in the presence of such dense hemorrhages that are also observed in the initial computed tomography scans of the head.

A coagulopathy and bleeding at a variety of sites including the brain are known to complicate severe perinatal herpesvirus infections and perinatal herpesvirus sepsis [7]. Bleeding in infants may reflect a combination of disseminated intravascular coagulation, hepatocellular damage with consequent insufficient production of clotting factors, and viral-induced thrombocytopenia [7]. Although disseminated herpesvirus infection with coagulopathy cannot be excluded as the preceding or co-existing event, the etiology of the coagulation dysfunction remains unclear. One week after her initial presentation with irritability and fevers and after the hypercoagulable state, our patient developed hepatosplenomegaly and a mild increase in her liver enzymes. These findings were thought to be a result of the use of high doses of acetaminophen and clindamycin and spontaneously resolved. Her blood viral cultures remained negative, and she had no further bleeding. To our knowledge, this is the first pediatric patient with herpes simplex encephalitis presenting with large areas of intracranial hemorrhage beyond the neonatal period.

Although our patient's presentation was atypical, her hospital course was characteristic for herpes simplex encephalitis. She initially lacked the temporal lobe involvement considered characteristic of herpes simplex encephalitis beyond the neonatal period. The signs of inflammation and petechial hemorrhages appeared after

the initial presentation with intracranial bleeding and a possible coagulopathic stage. The early presentation with severe bilateral intracranial hemorrhages in this patient may be a result of the co-existence of this coagulation abnormality with acute intense neuronal lysis after viral replication [8]. Acyclovir treatment was instituted on the first day of admission primarily because of the fevers and cerebrospinal fluid pleocytosis. There were no data on the expected cerebrospinal fluid findings of herpes simplex encephalitis at our patient's age, although the mildly elevated cerebrospinal fluid lymphocyte counts were within the reported range for infants [9]. The diagnosis of herpes simplex encephalitis was confirmed with a positive herpesvirus polymerase chain reaction.

We believe that this patient illustrates several important points about pediatric herpes simplex encephalitis. The polymerase chain reaction detection of DNA in the cerebrospinal fluid proved to be a sensitive and specific tool for the diagnosis of herpes simplex encephalitis; however, the most important factor in the diagnosis herpesvirus infection in our patient was the consideration of the diagnostic possibility [10,11]. This report also illustrated that herpes simplex encephalitis can present with large intracerebral hemorrhage.

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