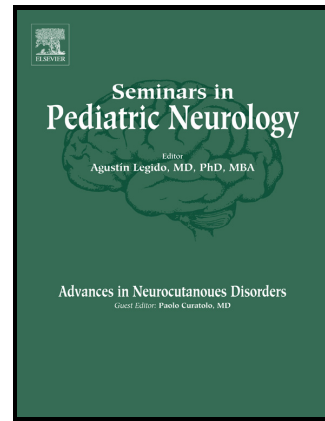


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A 20-Month-Old Girl with Fever, Seizures,
Hemiparesis and Brain Lesions Requiring a
Diagnostic Brain Biopsy

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Title: A 20-month-old girl with fever, seizures, hemiparesis and brain lesions requiring a diagnostic brain biopsy

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Abstract

We report a case of a 20-month-old girl with atypical presentation of a fairly common condition. She presented with acute onset of fever, seizures and hemiparesis. Her cerebrospinal fluid (CSF) showed total nucleated cells $10/\text{mm}^3$ with lymphocyte dominance. Herpes simplex virus (HSV) polymerase chain reaction (PCR) result was negative. Computed tomography (CT) of head showed a cerebral hemorrhage of the left frontal lobe and small subarachnoid hemorrhage

in right frontal region. Brain MRI revealed multiple foci of hyperintensity in bilateral parietal lobes and right basal ganglia. She remained clinically stable without a specific therapy. Her diagnosis was made after a brain biopsy.

Case Report

A 20-month-old girl presented with acute onset of fever, seizures and hemiparesis. Her past medical history was only remarkable for premature birth at 34 weeks by Caesarian section due to maternal preeclampsia. Her neonatal course was unremarkable. Developmentally, she was normal prior to the current illness. Her family and social history were unremarkable.

On day 1, she presented to a local emergency room with a brief generalized seizure and two-day history of rhinorrhea and fever. She was diagnosed with a febrile seizure associated with upper respiratory infection and was discharged home. On day 2, she had focal motor seizure involving her left face, arm and leg which lasted for one hour until she received diazepam in the local emergency room. She was loaded with phenobarbital. After resolution of the seizure, she was noted to have left hemiparesis. Computed tomography (CT) of head showed a cerebral hemorrhage of the left frontal lobe as well as a small subarachnoid hemorrhage in right frontal region. The imaging raised the concern for non-accidental trauma. Complete blood count with differential, C-reactive protein and coagulation panel were all normal. Bone survey and ophthalmologic exam were also unremarkable. She was admitted locally.

On day 3, she had another left sided focal motor seizure. Electroencephalogram (EEG) showed slow waves on the left central parietal region and focal epileptiform discharge in the right central region. Levetiracetam was added to phenobarbital with good seizure control. CSF obtained on day 3 showed total nucleated cells $10/\text{mm}^3$ (neutrophil 1, lymphocyte 6, monocyte 3), red blood

cells $9/\text{mm}^3$, protein 15 mg/dL, glucose 55 mg/dL. CSF stains (gram stain, fungal, mycobacterium) were negative for organisms. CSF HSV PCR and *Enterovirus* PCR were negative. MRI showed hemorrhage in the right frontal lobe and acute cortical changes at the right parietal vertex with subtle diffusion abnormality. MRI findings raised a concern for possible vasculitis. Erythrocyte sedimentation rate (ESR) and antinuclear antibody (ANA) were unremarkable. Magnetic resonance angiogram (MRA) of the head and magnetic resonance venogram (MRV) of the head were negative for vasculitis. Echocardiogram was normal. Broad-spectrum antimicrobials (vancomycin, ceftriaxone, and metronidazole) were started. Extensive infectious disease evaluation all came back negative (CSF studies including bacterial/fungal/mycobacterium cultures, *Histoplasma capsulatum* antibody, *Taenia solium* antibody, galactomannan. Blood and urine bacterial cultures. Blood fungal culture.)

She was transferred to our facility on day 8. Her physical examination was unremarkable except for left hemiparesis. Her mental status was normal. She had her second lumbar puncture on day 9 which showed elevated total nucleated cell count of $45/\text{mm}^3$ (neutrophils $0/\text{mm}^3$, lymphocytes $29/\text{mm}^3$, histiocytes $16/\text{mm}^3$) with red blood cells of $77/\text{mm}^3$. Because only small amount of CSF was obtained, CSF protein and glucose were not sent. Serum *Borrelia burgdorferi* antibody, serum *Toxocara canis* antibody and serum galactomannan were negative. Rheumatology was consulted for a concern of vasculitis, but workup including repeated brain MRA was essentially negative. Repeat brain MRI showed progressing cerebritis. Brain MRI [figure 1] revealed multiple foci of hyperintensity in bilateral cerebral hemispheres and right basal ganglia on fluid-attenuated inversion recovery (FLAIR) images with some enhancement on T1 post gadolinium sequences. These lesions were associated with restricted diffusion. Gradient echo (GRE) sequences suggested hemorrhage in more locations than appreciated on head CT [figure 2].

Brain biopsy was performed on day 9 given diagnostic uncertainty. This showed necrotizing hemorrhagic meningoencephalitis with positive immunostaining for HSV. In the face of positive immunostain result for HSV on the brain tissue, HSV PCR was added on the stored CSF sample obtained during the second lumbar puncture on day 9. The HSV PCR came back positive. Bacterial, fungal, acid-fast bacilli and viral cultures of the brain tissue were all negative.

Although her neurological condition appeared to be slightly improving despite the lack of antiviral therapy, acyclovir was started. The patient completed a 21 days of intravenous acyclovir. At one-month-follow up, she had residual mild left-sided hemiparesis and was seizure free on a low dose of levetiracetam.

Discussion

Herpes simplex encephalitis (HSE) is regarded as the most common cause of sporadic fatal encephalitis in patients > 6 months of age in the Western world. The incidence of HSE is ~1 case per 250,000 to 500,000 persons per year with one-third of cases occurring in children [1]. Early recognition and prompt antiviral therapy are critical to reduce morbidity and mortality. In the absence of effective antiviral therapy, the mortality for this encephalitis is >70%, with only 2-5% of individuals returning to normal function [2]. HSE is classically associated with fever, altered mental status and seizures with or without focal deficits. CSF often shows lymphocytic pleocytosis with elevated protein. On imaging, temporal lobe involvement is classically described [3].

Intranuclear inclusion bodies consistent with HSV infection were demonstrated first in the brain of a neonate with encephalitis in 1941 followed by the isolation of virus [4]. Brain biopsy is both sensitive and specific means of its diagnosis and remained as the “gold standard” until mid-1990’s. The availability of PCR has revolutionized the diagnosis of herpes simplex encephalitis.

It has allowed the definitive and rapid diagnosis of HSE, eliminating the need of routine brain biopsy [5-8].

Despite advances in diagnostic techniques including PCR and MRI, diagnosing HSE remains a challenge in some cases. Clinicians need to be aware of following caveats in the diagnosis of HSE.

Caveat 1: “non-specific” symptoms and “wide-range” in clinical presentations.

The clinical hallmark of HSE is fever, encephalopathy, seizures and focal neurologic symptoms. With wide use of HSV PCR, instead of brain biopsy, milder cases have been recognized [9,10]. Although early treatment with acyclovir is thought to be essential to reduce mortality and morbidity, some patients do not seem to deteriorate despite the lack of acyclovir treatment. There is even a report of two children aged 3.5 and 15 years who recovered fully without treatment with acyclovir [11]. Our case did not have encephalopathy and the patient was stable without clinical deterioration despite the lack of antiviral therapy for more than a week after presentation.

Caveat 2: “imperfect” CSF study including HSV PCR

In majority of patients with HSE, CSF shows pleocytosis with a lymphocytic predominance. The protein is usually elevated (mean 80mg/dL) and the glucose is often normal. However, normal CSF white cell count and protein does not rule out HSV encephalitis. CSF is normal on 5–10 percent of patients on initial lumbar puncture. Repeating the lumbar puncture at a later time will reveal abnormalities such as pleocytosis and elevated CSF protein in most cases [3]. Regarding CSF HSV PCR, a 1995 publication showed the overall sensitivity and specificity of 98 percent and 94 percent respectively resulting in a positive predictive value of 95 percent and a negative predictive value of 98 percent [12]. However further studies showed that the

sensitivity of PCR for detection of HSE varies with the timing of the study. There are reports of repeat CSF samples being positive for HSV PCR, after an initially negative CSF HSV PCR [13,14]. The rate of initially negative HSV PCR results is higher in pediatric patients, compared to 3 %~ 5 % reported for adults. Negative HSV PCR results, especially during the first 3 days of illness, does not exclude the diagnosis. It is prudent to repeat CSF study when clinically indicated [13].

Caveat 3: “temporal lobe” involvement

Although temporal lobe involvement is classic for HSE, extra-temporal lobe involvement is also seen both in adults and children [1, 15]. In our case, temporal lobes were not involved and lesions were in bilateral parietal lobes as well as unilateral basal ganglia.

Conclusion

In summary, HSE still can be a diagnostic challenge. It can have a wide range of clinical presentation with large differentials, non-specific CSF finding, false negative HSV PCR especially early in the course, and extra-temporal involvement, particularly in the infant. It is important to bear this information in mind when evaluating pediatric patients presenting with encephalitis.

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Figure 1: Multiple foci of hyperintensity on FLAIR images.

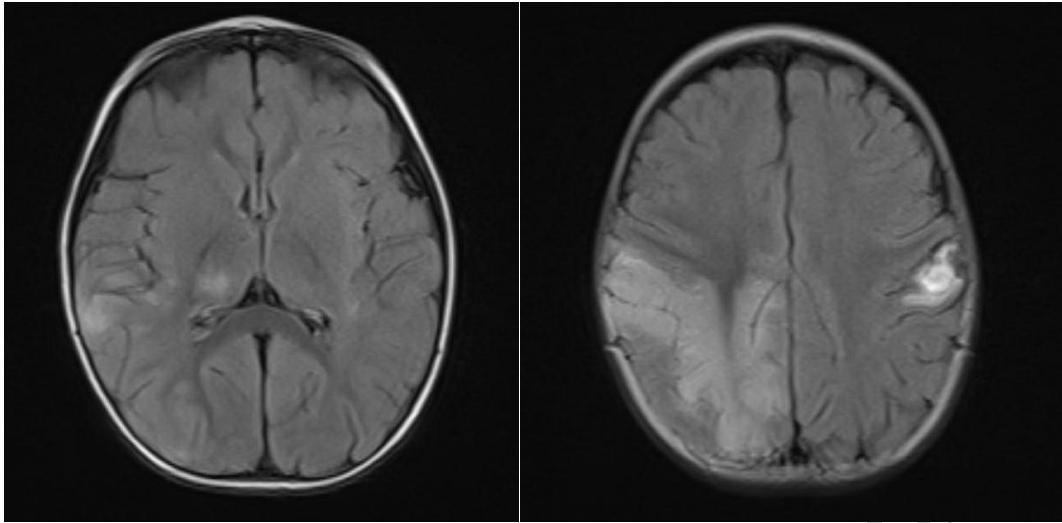


Figure 2: GRE sequence showing areas of hemorrhage.

