

## **Devastating Outcomes Following Herpetic Encephalitis**

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### **Abstract**

**Neurological complications following herpetic encephalitis are not uncommon, though devastating neurological deficits are uncommon complications of herpetic encephalitis. We describe 4 cases who presented with herpetic encephalitis that, despite receiving early therapy, passed through a progressive devastating course. We discuss the risk factors that may predispose patients to these complications and how to avoid their progression.**

**There are no clear data regarding the incidence of herpetic encephalitis in Saudi Arabia. It seems that the incidence is increasing with the emergence of post meningoencephalitic sequelae that need long term follow up and rehabilitation measures. We aim to raise a red flag for better management of herpetic encephalitis in a way to avoid devastating post herpetic encephalitis.**

**Key words: Herpes Simplex, encephalitis, outcomes.**

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### **Introduction**

Herpes simplex virus (HSV) infections of the central nervous system (CNS) are the most common cause of sporadic encephalitis, with an incidence of more than 2,000 cases annually in the United States.<sup>(1)</sup> An additional 1,500 cases occur as disseminated neonatal herpes simplex encephalitis, caused by HSV type 2, bringing the total burden of the serious disease to more than 3,500 cases per year.<sup>(2)</sup> Furthermore, atypical, and less severe cases of herpes simplex encephalitis bring this number towards a higher rate.<sup>(3)</sup> Recent data estimated an incidence of about 1 in 250,000 to 500,000 people per year and a third of cases occurring in children.<sup>(4)</sup>

Tremendous advances in the ability to diagnose HSV, coupled with the establishment of safe and effective antiviral therapies, have improved overall outcomes. However, the seriousness of HSV CNS infections requires that clinicians maintain a high index of suspicion to initiate evaluation and treatment under suitable circumstances. Intravenous Acyclovir remains the mainstay of antiviral management<sup>(5)</sup>, which decreases mortality dramatically from 75% to 25%.<sup>(1, 6 & 7)</sup>

A dramatic improvement of the survival rate and prognosis occurs if treatment is initiated very early after the on-

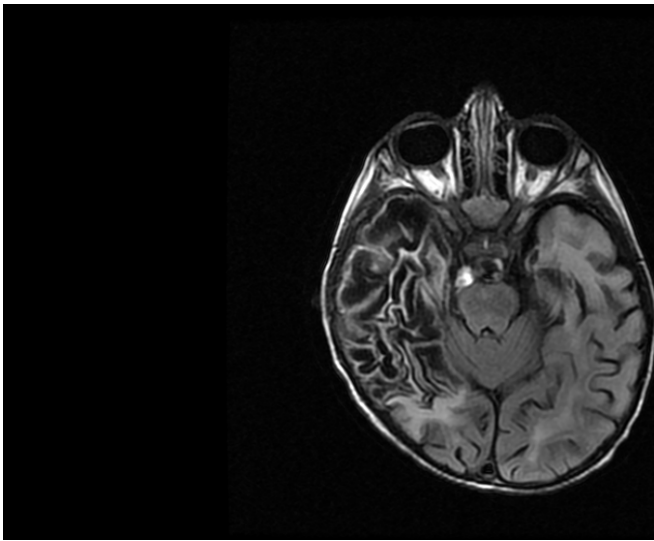
set of the disease. Early diagnosis is, therefore, crucial for predicting the outcome.<sup>(8)</sup>

Polymerase Chain Reaction (PCR) detection of HSV DNA is considered the gold standard to confirm HSV encephalitis with an estimated sensitivity of 96% and specificity of 99% for early diagnosis. Reports with false negative PCR results, with sensitivity reaching only 70%–75%. This fact could be related to the absence of HSV or the presence of a very low viral load in the CSF at the onset of an acute encephalitic process in children, may be due to the presence of heme and other inhibitors. If given early in the clinical course of HSE.<sup>(9)</sup>

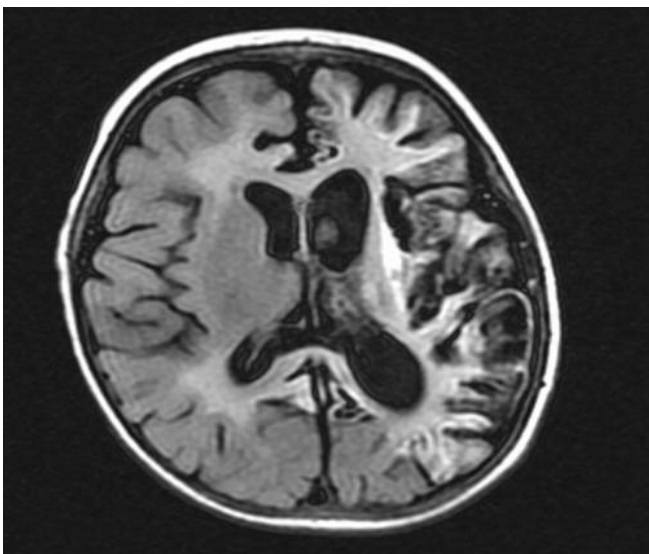
Acyclovir reduces both mortality and morbidity in treated patients. It should be administered at a dosage of 20mg/kg every 8 hours (60mg/kg/d) for a period of 21 days. Proper and immediate treatment of HSV encephalitis has proven to decrease neurological impairments in survivors, with many patients reporting minor or no neurological impairment at follow-up.<sup>(10)</sup>

### **Case I**

A two year and 6 months old boy presented with on and off fever; reaching 39-40 degrees Celsius; for one week followed by progressive decreased level of consciousness for one day. He was healthy until the age of 2 years and 5 months, when he suffered from high grade fever, vomiting, and attacks of generalized tonic clonic seizures. He



*Case I MRI shows diffuse hypo intensities in right Temporal, Parietal and Occipital lobes, as well as the splenium of the corpus callosum denoting extensive encephalomalacic changes with patchy meningeal enhancement.*



*Case II MRI showed diffuse hypo intensities in left Temporal, Parietal and Occipital lobes, as well as the dilatation of the left lateral ventricle.*

was admitted to a governmental hospital and received Acyclovir 60 mg/kg/day Intravenous (IV) and Ceftriaxone 100 mg/kg/day (IV) for 10 days. He showed some improvement and was discharged in stable condition.

Three days later, he spiked a fever again with altered level of consciousness and was seen in the King Fahad Medical City (KFMC) Emergency Room (ER). His past and family histories were non contributory and immunization was up-to-date.

He was admitted to the Pediatric Intensive Care Unit (PICU) for 1 week, and was negative for HSV PCR (CSF) and positive for HSV IgM 1, 2. The EEG exhibited markedly attenuated cerebral activity over the fronto temporal region. Clinically he was awake though unaware of his surroundings and a nasogastric tube (NGT) was placed due to poor swallowing but was later replaced by a gastrostomy tube.

Two weeks later, he developed generalized choreoathetoid movements and acquired an opisthotonus posture and intermittent dystonic reaction; Clonazepam and Diazepam were administered without improvement. He was transferred to the ward and evaluated by the Infectious Diseases (ID) team that decided to complete the course of Acyclovir and Ceftriaxone for 21 days. The Benadryl test improved his acute dystonic reaction, so he was started on Haloperidol (0.5 mg /kg/day) orally. This resulted in a marked reduction of his choreoathetoid movements (frequency, intensity, and duration). He received Haloperidol 35 mg intramuscular (IM) monthly for 6 months until his movements became under control and Haloperidol was tapered and stopped.

He is currently on continuous rehabilitative care and physiotherapy programs..

## Case II

A 10 month old girl presented with fever, right sided tonic clonic convulsion, and twitches on the right angle of the mouth for 30 minutes, which were relieved by 2 doses of rectal Diazepam in the ER. She developed right hemiparesis and was admitted to PICU. Her CSF showed WBC 14/ul (Mononuclear 93%, PNL 7%) but her CT Brain was unremarkable.

She was diagnosed as having atypical febrile seizures and was started on Phenytoin (PHT) and Ceftriaxone. She showed improvement and became fully conscious with no neurological deficit although she remained febrile. Two days later, she became drowsy, unable to sit steadily, and developed severe attacks of focal convulsion on the right side of her body which was relieved by Diazepam (IV). CSF PCR for HSV was ordered and she was given Acyclovir 30mg/kg/day (IV), Phenobarbitone (PB) 5 mg/kg/day, and PHT 4 mg/kg/day.

Her EEG showed continuous focal discharges over the left temporal lobe and her level of consciousness deteriorated with increased frequency of seizures. Carbamazepine 10mg/kg/day was added then stopped due to skin rashes and Levetiracetam (LVT) 10mg/kg/day was then introduced. The PCR test detected HSV-1 DNA.

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Three weeks later, she remained febrile and on NGT. Her CSF sample showed WBC 144/ul, 94% monocytes, and protein (2.48g/dl). Her CSF culture and sensitivity showed no growth after 3 days. On the 16<sup>th</sup> day, Acyclovir was increased to 45 mg/kg/day. She continued to be febrile with recurrent seizures. On the 18<sup>th</sup> day, Acyclovir was increased to 500mg/m<sup>2</sup>/8h. She stayed afebrile for 5 days and stable, although her seizures did not cease, so Topiramate was added. Then she became febrile again and her C-reactive protein (CRP) reached 48. She developed infantile spasms and was started on Vigabatrin 40mg/kg/day. She is now on five antiepileptic drugs and her seizures are still uncontrolled. However, synthetic ACTH was added which controlled her seizures.

### **Case III**

A two year and 6 month old boy came to our ER with a history of fever for one week, was being treated with Amoxicillin 40 mg/kg/day, and paracetamol 15mg/kg/dose. One day prior, he developed disturbed level of consciousness. His CSF revealed 17 WBCs with monocytes predominance (73%) and Lymphocytes (26%). He received Dexamethazone 0.15 mg/kg/dose every 6 hours, then Vancomycin 60 mg/kg/day, and Acyclovir 60 mg/kg/day were added.

He developed recurrent attacks of focal seizures in the form of twitching of the left side of his face, left side aversive seizures, followed by secondarily generalization. PHT was given initially, then Oxcarbazepine was started and PHT was tapered and stopped. He was unconscious, not fixating nor following and had intact cranial nerves (II-XII) with generalized hypotonia and diminished deep tendon reflexes. He was withdrawing to pain with a Glasgow Coma Scale of 9/15 initially, then it deteriorated to 7/15. He was intubated and admitted to the PICU.

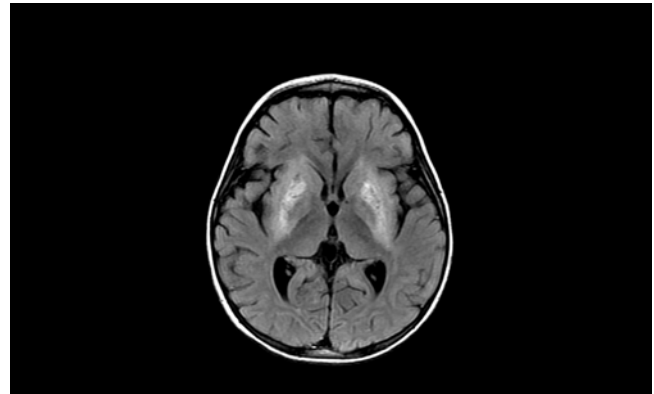
In the PICU, he was kept on a NGT, evaluated by the ID team who decided to complete the course of Acyclovir and Vancomycin for 21 days. He continued to spike a fever despite being on Vancomycin and Acyclovir (60mg/kg/day). He failed extubation three times.

Three weeks later, he started to show brain release phenomena in the form of lip smacking and chewing movements and he started to fix and follow objects. One week later, he was seen by an ENT team and found to have subglottic stenosis. A tracheotomy was performed and he was transferred to the ward.

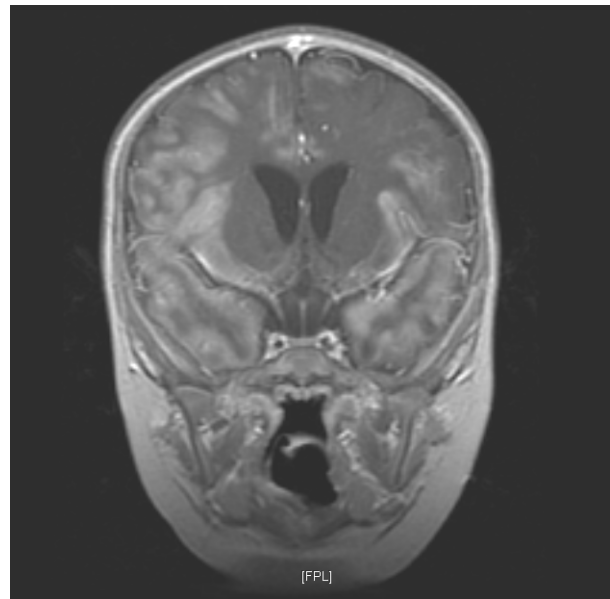
He developed a dystonic posture with excessive diaphoresis, hypertension, tachycardia, and continuous fever. A diagnosis of PAID (Paroxysmal Autonomic Instability Disease) was raised and Benadryl 1 mg/kg/dose was given every 6 hours for 2 days to temporarily reduce his acute dystonic reaction. Then Dantrolene 1 mg/kg/dose

IV was administered every 8 hours for 1 day, which controlled his dystonic reaction.

He received 80 unit Botulinum toxin injections in the right Para spinal muscle and 120 units in the left one which reduced his dystonic posture for approximately two weeks. He remained the same with cycles of Dystonia alternating with periods of normal tone and posture. He is currently receiving continuous rehabilitation measures.



*Case III MRI showed bilateral symmetrical hyperintensities occupying both basal ganglia.*



*Case IV MRI showed multi areas of high T2 signals intensities involving Temporal, Frontal and Occipital lobes more in the right, suggestive of Herpetic Meningoencephalitis with multiareas of Ecephalomalacia.*

### **Case IV**

A 9 month old male was transferred to our hospital as a case of post meningoencephalitic choreoathetosis, symptomatic epilepsy, and feeding difficulty on NGT feeding.

At the age of 7 months, he suffered from acute febrile illness for four days followed by focal seizures involving his face and his left upper limb. He was admitted to the hospital, received IV Ampicillin 40 mg/kg/day, Ceftriaxone 60 mg/kg/day, and PHT 10 mg/kg/day without control of his seizures. His parents refused to allow him to undergo a spinal tap at that time and his CT Brain was normal.

He was transferred to another hospital where he became unaware and developed squint, with intermittent mild stridor, and with increased deep tendon reflexes in his lower limbs. He was admitted to the PICU and got intubated and ventilated for 1 week. His CSF analysis showed 20 WBC. Lymphocytes were 80%, Neutrophils were 20%, high protein, with negative Latex and Gram stain. PCR CSF for HSV was Positive. Two CSF bacterial cultures were negative. Ceftriaxone 100mg/kg/day IV was started then Vancomycin 60mg/kg/day and Acyclovir 60mg/kg/day (28 days) were added.

His seizures were controlled by PHT 10mg/kg/day IV, PB 5mg/kg/day IV, and Midazolam 2ug/kg/min IV infusion which were tapered gradually after control of his seizures. His routine lab investigations, including blood culture, were normal. His second CSF analysis which was performed after 2 weeks showed no cells. His EEG showed slow background and no epileptogenic activity. His third CSF, taken after 2 weeks, showed a negative PCR for HSV and cultures were sterile. He became febrile and his blood culture was repeated and revealed "Candida Famata" which was also isolated from the tip of his central venous catheter. He received Amphotericin B 0.5 mg/kg/day (IV) (14 days) and the central venous catheter was removed and his fever subsided within 48 hours and he became stable. He began to tolerate food and 100 ml of Pediasure was given through his NGT and he was transferred to the ward.

Repeated blood culture, urine, and stool cultures were negative. He was seen by the pediatric neurologist who prescribed oral Baclofen 2.5 mg every 12 hours, oral PB 60 mg (6.4 mg/kg/day), and Clonazepam 200 microgram/day for his generalized dystonic movement. He was discharged from the hospital after 1 month.

He was transferred to our hospital, admitted to the ward, as a case of post meningoencephalitis choreoathetosis, gastro-oesophageal reflux disease, and NGT feeding and focal epilepsy controlled on PB 5mg/kg /day and Clonazepam 0.02 mg/kg /day. He was unaware of his surroundings, was unable to fixate, nor following with resolving left sided facial palsy. Examination of his motor system revealed normal tone, normal power, and normal deep tendon reflexes on the right side. Left side examination showed decreased power and increased deep tendon reflexes than his right side.

He was having these abnormal movements only when awake more on the right side with tongue thrusting with sialorrhoea. It was decided that Clonazepam was to be tapered gradually and LVT was started then increased to 15mg/kg/day after 5 days with an improvement of his dystonic movements. This was followed by starting a PB tapering schedule.

His OAE (Oto-Acoustic Emission) revealed normal cochlear function bilaterally and his ABR (Auditory Brainstem Response) revealed normal peripheral hearing sensitivity bilaterally. Further assessments by the swallowing team revealed improvement in his swallowing and he started taking oral feeds.

He was discharged on LVT 40 mg/kg/day and Baclofen 1.5 mg/kg/day and was transferred to a rehabilitation institute for continuous rehabilitative care.

## Discussion

Significant morbidity and devastating neurological deficits are still seen in cases of herpetic encephalitis which need a great level of suspicion in diagnosis to give the patient the benefit of early start of appropriate treatment for the appropriate duration. We do not have exact figures approximating the incidence of herpetic encephalitis in Saudi Arabia mainly due to lack of case reporting and the absence of a governmental regulation. Cases of herpetic encephalitis should be reported and other co-morbidities should be screened and treated promptly.

Acyclovir is still the first line of treatment, although the emergence of these and other cases world wide is raising a question: "Are we facing a newer (more virulent) strain of herpetic encephalitis?" There are other treatments for resistant herpes, for example Foscarnet and Cidofovir (IV) for Acyclovir-resistant herpes.<sup>(11)</sup> Other drugs are still under review, including Trifluorothymidine and Sorivudine, which may be effective weapons against these virulent strains we are facing these days.

Currently, no vaccine is available to prevent HSV infection in the pediatric population. Several HSV vaccines using varied methodologies are being studied and have demonstrated variable efficacy. Two separate phase 3 trials with an HSV-2gD vaccine demonstrated nearly 75% efficacy in preventing genital HSV disease and 38% efficacy in preventing HSV-2 infections in seronegative women.<sup>(12)</sup> No efficacy was demonstrated in men or in women who were HSV-1 positive before vaccination.<sup>(12)</sup>

HSE is an extremely rare complication that affects otherwise healthy children. This led to the hypothesis of a genetically determined susceptibility, inherited as a monogenic trait resulting in specific impairment of immunity to type 1 HSV. Until now, 2 mutations have been identified: a mutation of UNC93B and TLR3, both selectively affecting the production of type I interferon in response to type 1 herpes simplex virus infection. However, these 2 recognized gene defects account for only a small minority of childhood HSE and other mutations affecting the interferon production pathway in response to type 1 herpes simplex virus remain to be determined.<sup>(13)</sup> Animal studies have postulated that the presence and extent of white matter lesions with HSE are dependent on the immune status of the host, which may be genetically determined. Nevertheless, there are not any reports linking these 2 observations in humans and the follow-up of a large cohort of children presenting type I interferon production defect and associated herpes simplex encephalitis did not identify an over representation of these “relapses.”<sup>(14)</sup>

Extratemporal involvement in HSV encephalitis is not rare. In evaluating 88 patients with HSV encephalitis, extra-temporal lesions were present in 55% of them, where in only 3 cases there was not an associated involvement of temporal lobes.<sup>(9)</sup>

Relapse of herpes simplex virus encephalitis after completion of conventional acyclovir therapy has been infrequently reported in children. Early relapse occurs within several weeks after the safe completion of antiviral treatment, while late relapse usually occurs more than 3 months (sometimes even years) after the initial encephalitic episode. Previous studies estimated early relapse rate of 27%. Several mechanisms have been suggested to explain early relapse, including late-onset symptoms of the initial viral infection, recurrence of viral replication due to incomplete treatment of the initial episode, and induction of an immune-inflammatory reaction similar to that observed in post-infectious encephalitis. Late relapse of herpes simplex virus encephalitis, although uncommon in children, may occur even many years after the primary infection by the herpes simplex virus, and in most cases, it is the result of latent virus reactivation. Clinical, radiological, and neuro-pathological characteristics are similar to those of the primary infection<sup>(15)</sup>

Post herpetic complications varied from acute ascending necrotizing myelitis<sup>(16)</sup>, acute retinal necrosis (ARN) which was reported several years after neonatal and infantile herpetic encephalitis. Therefore, herpetic encephalitis may be a risk factor for ARN development, HSV virus accesses the retina from the brain by the trans-axonal route; consequently, it can cause recurrent episodes of ARN.<sup>(17)</sup> ARN may be an indication of possible CNS involvement and neuroimaging may be necessary in all cases of ARN to rule out herpetic encephalitis.<sup>(18&19)</sup>

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