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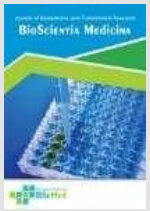

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Navigating Diagnostic Constraints in Pediatric Herpes Simplex Encephalitis: Successful Empirical Acyclovir Therapy without PCR Confirmation

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A B S T R A C T

Background: Herpes simplex encephalitis is an acute or subacute disease associated with focal or global cerebral dysfunction caused by herpes simplex virus type 1 or type 2. Without adequate antiviral administration, the mortality rate reaches 70 percent, with only 9 percent of survivors returning to normal function. While cerebrospinal fluid polymerase chain reaction testing is the gold standard for diagnosis, its availability is severely restricted in resource-limited clinical environments. **Case presentation:** We report the case of a 4-year-old girl who presented with a profoundly decreased level of consciousness following a five-day history of fluctuating fever. Physical examination revealed a soporific state with a Glasgow Coma Scale of E4V1M1. Initial non-contrast computed tomography of the head was unremarkable. Cerebrospinal fluid analysis demonstrated a mononuclear pleocytosis. Despite the lack of polymerase chain reaction confirmation and the absence of advanced electrophysiological monitoring, the patient was empirically diagnosed with herpes simplex encephalitis based on clinical deterioration and cerebrospinal fluid findings. Immediate management included intravenous acyclovir, dexamethasone, phenobarbital, and supportive care. The patient demonstrated significant clinical improvement and was discharged on day 24 without severe immediate neurological deficits. **Conclusion:** The absence of molecular diagnostics and advanced neuro-monitoring must not delay the administration of intravenous acyclovir in pediatric patients exhibiting fever and altered mental status. Empirical antiviral intervention remains the most critical determinant of survival and neurological recovery.

1. Introduction

The herpes virus is a double-stranded DNA virus, eight types of which can infect humans. This virus has been studied extensively, with clinical descriptions appearing even in ancient Greek literature.[1] Among the most devastating clinical manifestations of this viral family is herpes simplex encephalitis, which presents as an acute or subacute disease associated with focal or global cerebral dysfunction. The infectious etiology is primarily attributed to herpes simplex virus type 1 or type 2. Epidemiological data and virological surveillance indicate that most cases of herpes simplex encephalitis are caused by herpes simplex virus type 1, with herpes simplex virus type 2 accounting for less than 10 percent of the overall disease burden. Specifically, post-neonatal herpes encephalitis is predominantly caused by herpes simplex virus type 1, which is recognized globally as the most common cause of fatal sporadic and non-seasonal encephalitis. Conversely, neonatal herpes encephalitis can be caused by either type, although type 2 is more common and often involves the brain more globally, resulting in more severe neurological sequelae.[2]

Herpes simplex infection of the central nervous system represents one of the most serious and

catastrophic viral infections of the human brain.[3] The virus can attack individuals of all ages, regardless of gender, with a notable predilection for the pediatric demographic and the elderly population. The global incidence ranges from 1 in 250,000 to 500,000 people per year.[4] Without adequate and rapid antiviral administration, the natural history of the disease is grim; the mortality rate reaches 70 percent, with merely 9 percent of survivors being able to return to normal neurological and physiological function after the acute illness. This high morbidity and mortality necessitate a rapid and accurate diagnosis in pediatric patients suspected of having central nervous system infections.[5]

In well-resourced international healthcare systems, the herpes simplex virus polymerase chain reaction test performed on cerebrospinal fluid is established as the gold standard for definitive diagnosis. This molecular diagnostic tool provides high sensitivity and specificity, allowing for targeted pharmacotherapy.[6] However, in many developing nations and resource-limited regions, including various parts of Indonesia, polymerase chain reaction testing for herpes simplex in cerebrospinal fluid is not a routine test readily available in regional hospitals. Furthermore, laboratory facilities are often strictly limited, and the cost of advanced molecular testing is prohibitively high for the vast majority of the patient population. Specialized diagnostic modalities like continuous electroencephalographic monitoring are similarly absent in these peripheral care centers, forcing clinicians to rely entirely on basic laboratory parameters and sharp clinical acumen.[7]

Due to these severe diagnostic limitations, clinical practice must rely heavily on established protocols and empirical judgment. Various medical consensus statements and neurological guidelines agree that children suspected of having encephalitis should immediately receive intravenous acyclovir if the initial cerebrospinal fluid investigation and clinical imaging results favor a viral etiology.[8] Management of encephalitis in these settings is a profound clinical challenge given the rapid progression of neuronal necrosis and the intense need for critical care monitoring.[9] Even if initial cerebrospinal fluid microscopy and imaging results are entirely normal, therapeutic guidelines dictate that acyclovir should still be administered within the first 6 hours of treatment if there is a strong clinical suspicion of the disease while awaiting any further diagnostic confirmation. The prognosis for untreated patients is exceedingly poor, whereas early empirical treatment with acyclovir has been shown to reduce mortality to 28 percent.[10]

The primary aim of this study is to detail the clinical presentation, diagnostic triage, and successful empirical pharmacological management of a severe pediatric case of suspected herpes simplex encephalitis in a regional hospital lacking advanced molecular diagnostics and specialized neuro-monitoring. The novelty of this study lies in its comprehensive documentation of a successful clinical protocol utilizing standard cerebrospinal fluid analysis, careful clinical triaging, and aggressive empirical acyclovir up-titration to achieve complete neurological recovery, providing a vital evidence-based framework for clinicians operating in similarly resource-constrained environments globally.

2. Case Presentation

Ethical consent statement

This case report was conducted in strict adherence to the fundamental principles outlined in the Declaration of Helsinki regarding medical research involving human subjects. Prior to the initiation of any clinical data extraction or manuscript preparation, formal ethical approval was obtained from the Institutional Review Board and the local ethical committee of the participating regional hospital. Given that the subject of this medical report is a pediatric patient, comprehensive written informed consent was acquired directly from the patient’s parents. The parents were thoroughly briefed on the scientific purpose of the publication and subsequently provided explicit written authorization for the dissemination of the patient's clinical details, laboratory findings, and

relevant medical history within an academic medical journal. To ensure absolute patient privacy and uphold confidentiality mandates, all personally identifiable information has been rigorously anonymized or entirely redacted. The authors unconditionally affirm their commitment to maintaining the highest ethical standards.

Patient history and clinical presentation

A 4-year-old girl was urgently referred from Klungkung Regional General Hospital to the Pediatric Department of Sanjiwani Regional General Hospital, Gianyar, Bali, Indonesia. The patient presented with a chief complaint of a profoundly decreased level of consciousness that had commenced one day prior to admission. According to the collateral history provided by the parents, the patient was still able to talk and communicate during the morning of the previous day before experiencing a rapid and unprovoked neurological decline.

The history of the present illness revealed that the patient had suffered from a fluctuating high-grade fever for the previous five days. Over the preceding two days, her appetite and oral fluid intake had decreased significantly. This reduction in fluid intake led to a state of clinical dehydration, evidenced by her last recorded urination occurring at 3:00 p.m. on the day prior to her transfer. The comprehensive medical history was carefully reviewed; the patient's family explicitly denied any previous complex medical history, recent physical trauma, or any incidents of animal bites, which critically aided in lowering the clinical suspicion for rabies.

Physical and neurological examination

Upon admission to the emergency department, a thorough physical examination was conducted. The patient's general condition was assessed as profoundly weak and soporific. Her level of consciousness was quantified using the Glasgow Coma Scale, which yielded a critically low score of E4V1M1, indicating spontaneous eye opening but absent verbal and motor responses to stimuli.

Vital signs were meticulously recorded: her blood pressure was 94/60 mmHg, her pulse was 70 beats per minute with a regular and strong lift, and she exhibited tachypnea with a respiratory rate of 20 times per minute. Her axillary temperature was significantly elevated at 38.6°C, confirming a state of hyperpyrexia. Oxygen saturation was maintained at 100 percent while receiving supplementary oxygen via a nasal cannula at 2 liters per minute. Her measured body weight was 18 kg.

The general systemic examination yielded mostly normal findings. Both eyes appeared non-anemic, there was no clinical evidence of scleral icterus or jaundice, and her pupils were isochoric with a symmetric diameter of 2 mm, exhibiting a sluggish reaction to light. Thoracic examination of the cardiovascular system revealed a single regular heart sound, specifically S1 and S2, with no audible murmurs or gallops. Pulmonary auscultation demonstrated clear vesicular breath sounds bilaterally, and no adventitious sounds such as rhonchi or wheezing were detected. Abdominal examination showed bowel sounds within normal limits, a lack of visible distension, and no palpable tenderness or organomegaly. Examination of the upper and lower extremities revealed warm acral areas with a capillary refill time of less than two seconds, and no peripheral edema was noted. Dermatological evaluation later revealed widespread hypopigmented macules across her torso, clinically consistent with tinea versicolor.

A targeted neurological assessment was performed. Notably, meningeal signs were absent, as no stiff neck was found upon passive flexion. Evaluation of cranial nerves VII and XII was exceedingly difficult to perform accurately due to the patient's soporific state and inability to follow commands. On motor examination, no clear lateralization or focal deficits could be observed. Assessment of physiological reflexes revealed a positive right and left biceps reflex graded as 2, and a positive right and left knee patellar reflex graded as 2. Pathological reflex examinations, including Hoffman's, Trömner's, and Babinski tests,

were definitively negative on both the right and left sides. Based on the comprehensive medical history and the findings of the physical examination, the initial working diagnosis was a severely decreased level of consciousness secondary to infectious encephalitis, compounded by a continuous fever on day 5 of illness.

Table 1. Summary of Clinical Findings of Patient on Admission

CATEGORY	PARAMETER	CLINICAL FINDING
PATIENT DEMOGRAPHICS & HISTORY	Age / Sex / Weight	4 years / Female / 18 kg
	Chief Complaint	**Profoundly decreased level of consciousness (since 1 day prior)**
	Prodromal Symptoms	Fluctuating fever (5 days), decreased appetite and oral fluid intake (2 days), oliguria
VITAL SIGNS	Blood Pressure	94/60 mmHg
	Heart Rate	70 beats per minute (regular, strong lift)
	Respiratory Rate	20 breaths per minute (tachypnea)
	Temperature (Axillary)	**38.6°C (Hyperpyrexia)**
	Oxygen Saturation (SpO2)	100% (on nasal cannula 2 liters per minute)
NEUROLOGICAL STATUS	Glasgow Coma Scale (GCS)	**E4V1M1 (Soporific)**
	Meningeal Signs	Absent (no nuchal rigidity/stiff neck)
	Pupillary Assessment	Isochoric, 2 mm diameter, sluggish reaction to light bilaterally
	Motor Function	No clear lateralization or focal deficits observed
	Reflexes	Physiological: Biceps (+2), Patellar (+2) bilaterally. Pathological: Hoffman, Trömner, Babinski negative bilaterally.
GENERAL SYSTEMIC EXAMINATION	Cardiovascular	Single regular heart sounds (S1, S2), no murmur, no gallop
	Pulmonary	Vesicular breath sounds bilaterally, no rhonchi, no wheezing
	Gastrointestinal	Normoactive bowel sounds, no visible distension, no tenderness, no organomegaly
	Extremities	Warm acral areas, capillary refill time less than 2 seconds, no peripheral edema
	Dermatological	Widespread hypopigmented macules across torso (consistent with tinea versicolor)

Diagnostic workup

To support the clinical diagnosis and direct the therapeutic strategy, an extensive battery of laboratory tests and imaging studies was ordered.

Hematological and biochemical profiles: The results of the complete blood count and peripheral

blood examination demonstrated mild hematological shifts. The examination revealed a hemoglobin level of 9.6 g/dL (reference 11.0-16.0), a hematocrit of 27.6 percent (reference 35.0-49.0), and a red blood cell count of 3.44x10⁶/µL (reference 3.50-5.50). The total white blood cell count was 5.74x10³/µL (reference 4.00-12.00). The leukocyte differential count showed neutrophils at 74.6 percent (reference 25.0-70.0), absolute neutrophils at 4.29x10³/µL, lymphocytes at 14.8 percent (reference 20.0-65.0), and absolute lymphocytes at 0.85x10³/µL. Additional indices included a platelet count of 182x10³/µL, mean corpuscular volume of 80.4 fL, and mean corpuscular hemoglobin of 27.9 pg (Table 2).

Clinical chemistry evaluations revealed mild derangements. Liver transaminases were within normal limits, with an SGOT of 20 U/L (reference <35) and an SGPT of 7 U/L (reference <41). Renal function markers demonstrated a slightly decreased urea level of 11.1 mg/dL (reference 18-55) and a creatinine level of 0.31 mg/dL (reference 0.2-0.7). Serum electrolyte profiling indicated a state of mild hyponatremia with a sodium level of 129 mmol/L (reference 132-145), alongside a potassium level of 3.4 mmol/L (reference 3.5-5.0) and a chloride level of 105 mmol/L. Random blood glucose was measured at 118 mg/dL.

Table 2. Summary of Hematology and Clinical Chemistry Findings

CATEGORY	PARAMETER	RESULT	REFERENCE RANGE
HEMATOLOGY & PERIPHERAL BLOOD	Hemoglobin (HGB)	9.6 g/dL (Mild Anemia)	11.0 - 16.0 g/dL
	Hematocrit (HCT)	27.6%	35.0 - 49.0%
	Red Blood Cells (RBC)	3.44 x 10^6/µL	3.50 - 5.50 x 10^6/µL
	White Blood Cells (WBC)	5.74 x 10^3/µL	4.00 - 12.00 x 10^3/µL
	Neutrophils	74.6% (4.29 x 10^3/µL)	25.0 - 70.0%
	Lymphocytes	14.8% (0.85 x 10^3/µL)	20.0 - 65.0%
	Platelets (PLT)	182 x 10^3/µL	150 - 450 x 10^3/µL
	Mean Corpuscular Volume (MCV)	80.4 fL	80.0 - 100.0 fL
	Mean Corpuscular Hemoglobin (MCH)	27.9 pg	27.0 - 34.0 pg
CLINICAL CHEMISTRY & ELECTROLYTES	Serum Glutamic Oxaloacetic Transaminase (SGOT)	20 U/L	< 35 U/L
	Serum Glutamic Pyruvic Transaminase (SGPT)	7 U/L	< 41 U/L
	Urea	11.1 mg/dL	18 - 55 mg/dL
	Creatinine	0.31 mg/dL	0.2 - 0.7 mg/dL
	Sodium	129 mmol/L (Hyponatremia)	132 - 145 mmol/L
	Potassium	3.4 mmol/L	3.5 - 5.0 mmol/L
	Chloride	105 mmol/L	96 - 111 mmol/L
	Random Blood Glucose	118 mg/dL	80 - 120 mg/dL

Neuroimaging: On August 4th, 2023, the patient underwent an urgent non-contrast computed tomography scan of the head. A rapid radiological assessment was imperative to rule out space-occupying lesions, gross cerebral edema, or intracranial hemorrhage prior to performing a lumbar puncture. The imaging results showed absolutely no abnormal hypodense or hyperdense lesions within the brain parenchyma. The density of the white and gray matter was entirely within normal limits, and there was no evidence of a midline shift. Furthermore, the ventricular and subarachnoid systems, paranasal sinuses, sulci, gyri, and scanned orbits were all completely within normal anatomical limits, and the cranial vault bones were intact. An anteroposterior chest radiograph was also performed, which showed the heart and lungs to be within normal physiological limits.

Cerebrospinal Fluid Analysis: Following the clearance from the computed tomography scan, a lumbar puncture was successfully performed. The macroscopic evaluation of the cerebrospinal fluid showed it to be cloudy in color, deviating from the normal clear appearance. Cytological analysis revealed a significant pleocytosis with a white blood cell count of 960 cells/µL. The cellular differential demonstrated a massive mononuclear cell predominance of 94 percent, while polymorphonuclear cells accounted for only 6 percent. Biochemical analysis of the fluid showed a normal glucose concentration of 62 mg/dL against the serum glucose of 118 mg/dL, and an elevated protein concentration of 0.08 g/dL (reference 0.15-0.45). Qualitative globulin tests, specifically the Pandy and Nonne tests, returned negative results (Table 3).

Table 3. Summary of Cerebrospinal Fluid Analysis and Radiological Imaging

CATEGORY	PARAMETER	RESULT	REFERENCE RANGE
CEREBROSPINAL FLUID (CSF) ANALYSIS	Macroscopic Appearance	Cloudy	Clear / Colorless
	WBC Cell Count	960 cells/µL (Pleocytosis)	0 - 20 cells/µL
	Differential Count	94% Mononuclear 6% Polymorphonuclear	Predominantly Mononuclear (normally)
	CSF Protein	0.08 g/dL	0.15 - 0.45 g/dL
	CSF Glucose	62 mg/dL	45 - 70 mg/dL
	Globulin (Pandy & Nonne)	Negative	Negative
RADIOLOGICAL IMAGING	Non-Contrast CT Scan (Head)	No abnormal hypodense/hyperdense lesions. White/gray matter density within normal limits. No midline shift. Ventricular systems, paranasal sinuses, sulci, and gyri within normal limits.	
	Anteroposterior Chest X-Ray	Cor and pulmo within normal physiological limits.	

Clinical course and therapeutic interventions

Initial stabilization efforts began at Klungkung Regional Hospital, where the patient was administered intravenous fluid therapy with Ringer's Lactate at 12 drops per minute, paracetamol syrup for pyrexia control, and a slow intravenous bolus of diazepam 5 mg to manage potential seizure activity.

Upon admission to the intensive care unit at Sanjiwani Regional General Hospital, a robust and comprehensive empirical treatment protocol was immediately deployed. The patient received supplemental oxygen via a nasal cannula at 2 liters per minute and intravenous fluid hydration utilizing D5 1/2 NS at a macro drip rate of 18 drops per minute.

Fever was managed aggressively with intravenous paracetamol 20 ml administered every eight hours as needed. To mitigate severe cerebral inflammation, an initial slow intravenous bolus of dexamethasone at a dose of 10 mg was given, followed by a continuous maintenance dose of 7.5 mg intravenously every eight hours (Table 4).

During her acute care at Sanjiwani Regional General Hospital, the patient experienced a severe episode of generalized seizure activity. The clinical manifestation involved upward rolling of the eyes, accompanied by bilateral stiffness and rigidity in both her upper and lower extremities. This necessitated immediate anticonvulsant therapy. Phenobarbital was utilized, starting with a loading dose of 180 mg diluted in 30 cc of 0.9 percent NaCl administered via a 30-minute drip, followed 12 hours later by a maintenance dose of 45 mg intravenously twice a day. Due to the high risk of respiratory compromise from the central nervous system infection and the sedating effects of the anticonvulsants, backup non-invasive ventilation was fully prepared and stationed at the bedside.

Broad-spectrum antimicrobial coverage was initiated using an intravenous drip of ceftriaxone at a dose of 1 gram twice daily to cover potential bacterial meningoencephalitis. Gastrointestinal stress ulcer prophylaxis was provided through the administration of ranitidine 20 mg intravenously twice a day. Nutritional support was commenced via a nasogastric tube, initially with clear water starting at 10 cc every 3 hours, which was subsequently advanced to standard milk formula as tolerance was confirmed.

Once the results of the lumbar puncture were finalized, showing a distinct mononuclear predominance highly suspicious for a primary viral infection, specific antiviral pharmacotherapy was urgently added to the regimen. Intravenous acyclovir was initiated at a dose of 200 mg every eight hours. Additionally, the dermatological presentation of tinea versicolor was treated with topical ketoconazole cream applied twice daily.

Table 4. Summary of Diagnosis and Acute Treatment

PHASE	PARAMETER	DETAILS & CLINICAL NOTES
DIAGNOSTIC FORMULATION	Primary Diagnosis	**Herpes Simplex Encephalitis (Presumptive / Empirical)**
	Secondary Diagnoses	Status epilepticus (secondary to encephalitis), mild clinical dehydration, hyponatremia, and tinea versicolor.
ACUTE PHARMACOLOGICAL & SUPPORTIVE TREATMENT	Antiviral Therapy	• **Intravenous Acyclovir:** Initiated at 200 mg every 8 hours. • Dose up-titrated to 250 mg every 8 hours on day 10 for optimal viral clearance. • Administered continuously for 21 days.
	Anticonvulsant Therapy	• **Phenobarbital:** Loading dose 180 mg IV over 30 min, followed by maintenance 45 mg IV twice daily. • **Diazepam:** 5 mg slow IV bolus (utilized for acute seizure abortion).
	Corticosteroids	• **Dexamethasone:** Initial 10 mg IV bolus, then 7.5 mg IV every 8 hours. • Tapered to 5 mg IV every 8 hours on day 9.
	Antimicrobial & Topical	• **Ceftriaxone:** 1 gram IV twice daily (empirical coverage). • **Ketoconazole Cream:** Applied twice daily for tinea versicolor.
	Supportive Care	• Oxygen therapy (nasal cannula 2 lpm), backup non-invasive ventilation ready. • Intravenous hydration (D5 1/2 NS at 18 drops/min). • Paracetamol 20 ml IV every 8 hours for hyperpyrexia. • Ranitidine 20 mg IV twice daily for stress ulcer prophylaxis. • Nasogastric tube feeding (graduated from clear water to standard milk).

Outcome and follow-up

The clinical trajectory of the patient was closely monitored (Table 5). By the 4th day of intensive treatment, a noticeable and significant clinical improvement was documented. Although the patient still reported feeling generalized weakness, she began to actively respond to verbal stimuli from her parents using purposeful hand gestures, indicating a resolution of the profound encephalopathic state.

On the 9th day, the dexamethasone dosage was successfully tapered down to 5 mg intravenously every eight hours. By the 10th day, the intravenous acyclovir dose was deliberately increased to 250 mg every eight hours to optimize central nervous system viral clearance. The patient's neurological status continued to stabilize. Consequently, on the 13th day of admission, the intravenous therapies of dexamethasone, phenobarbital, and ranitidine were safely discontinued. To maintain seizure prophylaxis, the patient was transitioned to an oral regimen of valproic acid at a dose of 4 ml twice daily.

On the 21st and 22nd days of hospitalization, having completed a robust and sufficient course of empirical therapy, the acyclovir, ceftriaxone, and continuous intravenous fluids were definitively stopped. The patient exhibited an outstanding clinical recovery with an absence of gross residual motor deficits or recurrent seizure activity. She was deemed medically stable and was allowed to go home on the 24th day of treatment. Her comprehensive discharge medication regimen included oral valproic acid 4 ml twice daily, a daily folic acid supplement, and standard pediatric nutritional milk. The final confirmed clinical diagnosis was a decreased state of consciousness and convulsions strongly suspected to be due to herpes simplex encephalitis, alongside tinea versicolor.

Table 5. Summary of Clinical Follow-up and Final Outcome

PHASE	PARAMETER	DETAILS & CLINICAL NOTES
CLINICAL FOLLOW-UP & TIMELINE	**Day 1 - 3 (Acute Phase)**	Soporific state (GCS E4V1M1). Experienced a generalized tonic-clonic seizure requiring immediate abortive therapy and anticonvulsant loading.
	Day 4 (Initial Recovery)	**Significant clinical improvement.** Lethargy abated; patient began responding to verbal stimuli with purposeful hand gestures.
	Day 9 - 10 (Therapy Adjustment)	Dexamethasone tapered successfully. Intravenous acyclovir dose increased to maximize therapeutic efficacy.
	Day 13 (De-escalation)	Intravenous dexamethasone, phenobarbital, and ranitidine discontinued. Patient successfully transitioned to oral seizure prophylaxis (Valproic acid 4 ml twice daily).
	Day 21 - 22 (Therapy Completion)	Completed empirical antiviral course. Intravenous acyclovir, ceftriaxone, and continuous intravenous fluids definitively stopped.
FINAL OUTCOME & DISCHARGE	**Clinical Status at Discharge (Day 24)**	**Outstanding clinical recovery. No gross residual motor deficits observed. No recurrent seizure activity. Stable and interactive.**
	Discharge Regimen	• Oral Valproic acid 4 ml twice daily. • Folic acid supplement 1 tablet daily. • Standard pediatric nutritional milk. • Strict outpatient pediatric neurology follow-up.

3. Discussion

The successful management and favorable outcome of this severe pediatric case underscore several critical and complex pathophysiological, pharmacological, and diagnostic principles regarding herpes simplex encephalitis, particularly when navigating the formidable constraints of limited medical infrastructure. The precise molecular and anatomical mechanisms by which the herpes simplex virus successfully breaches the robust defenses of the central nervous system remain a subject of intense scientific investigation, yet three primary pathways of neuroinvasion are currently hypothesized in the literature.[11]

The brain is thought to be infected through local neural spread from a peripheral location or, less commonly, in older children, through systemic viremia (Figure 1). The first established pathway involves a primary oropharyngeal infection where the virus enters the mucosal epithelium. From this site, the virus ascends via retrograde axonal transport along the trigeminal or olfactory nerves, passing through the tentorial branch of the trigeminal nerve, penetrating the dura mater, and directly invading the frontal or temporal cortices. The second mechanism involves the virus establishing a state of latency within the trigeminal ganglion following an initial peripheral infection. Upon exposure to physiological or immunological stress, the virus reactivates and travels via anterograde transport along the same neural pathways to enter the brain. The final mechanism is driven strictly by the in situ reactivation of latent herpes simplex virus type 1 that has already established residence directly within the brain tissue itself. While profound viremia is commonly reported as the primary driver of central nervous system infection in neonates and immunocompromised patients, primary infection via neural tracking is the predominant cause of encephalitis in most pediatric patients outside the neonatal period.[12]

Once the virus successfully infiltrates the cerebral parenchyma, it demonstrates a highly specific and destructive predilection for the frontal and temporal lobes. The cytopathic effect of the virus is catastrophic. Herpes simplex virus type 1 actively induces apoptosis within the affected neuronal and glial cells, which inevitably leads to programmed cell death.[13] The virus subsequently infects the limbic system and rapidly spreads to both sides of the brain. This aggressive viral replication initiates a massive, localized host immune response, resulting in profound inflammation, severe cerebral edema, and ultimately hemorrhagic necrosis in the affected anatomical areas within a period of three weeks. The severe, generalized tonic-clonic seizures observed during the clinical course of our patient directly correlate with this highly epileptogenic cortical inflammation and necrosis. Manifestations of encephalitis often begin subtly with headaches, nausea, vomiting, personality changes, and memory impairments—symptoms that are exceptionally difficult to detect accurately in young children. The disease then rapidly progresses; patients experience acute seizures, localized neurological deficits, and a rapidly decreasing level of consciousness. Generalized seizures in this condition may be preceded by focal seizures that affect only a specific, highly localized area of the brain before progressing to generalized seizures that overwhelm the entire cerebral cortex. If these focal seizures are very brief in duration, parents and caregivers are often completely unaware of the symptoms. The aggressive nature of this pathophysiology explains why approximately 40 percent of patients arrive at the hospital already in a comatose state, while the remainder are severely lethargic.

The clinical diagnosis of herpes simplex encephalitis is incredibly challenging, as it relies initially on history taking, physical examinations, and supporting tests.[14] The clinical manifestations are notoriously non-specific, particularly in pediatric populations, meaning that the diagnosis requires an exceptionally strong index of clinical suspicion. The most frequently encountered physical examination findings are a high fever and acute changes in mental status. While comprehensive neurological examinations often show the presence of hemiparesis,

some complex cases can present with dysphasia, profound ataxia, autonomic system disorders, specific cranial nerve paresis, severe visual field defects, and papilledema of the optic nerve. Occasionally, the clinical presentation almost perfectly mimics aseptic meningitis without any clear, defining manifestations of deep encephalitis.

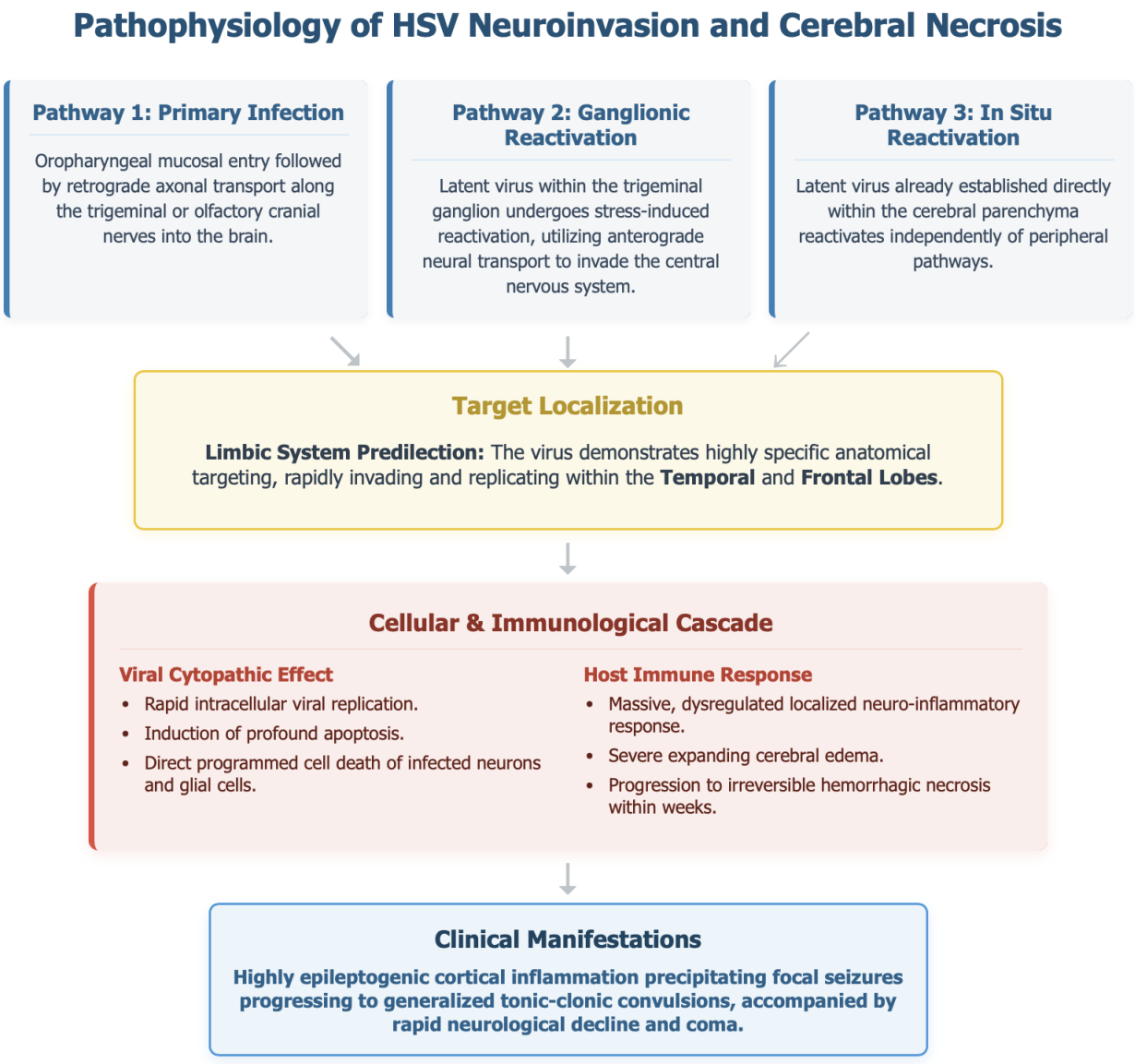

Figure 1. Pathophysiology of HSV neuroinvasion and cerebral necrosis.

Because there is absolutely no single pathognomonic clinical picture of herpes simplex encephalitis, diagnostic examinations must be expedited rapidly without ever delaying life-saving treatment.[15] From a practical standpoint, clinicians must always consider the possibility of this disease when encountering a child presenting with fever, new-onset seizures—especially focal seizures—and other focal neurological symptoms combined with a progressive loss of consciousness.

Laboratory diagnostics serve to support, rather than definitively confirm, the clinical suspicion in

resource-limited settings. Routine peripheral blood examinations are highly non-specific. The leukocyte count in the peripheral blood may be completely normal or only slightly elevated, sometimes showing a subtle left shift. Focal neurologic deficits, specific findings on computed tomography or magnetic resonance imaging, and distinct cerebrospinal fluid changes may take considerable time to clinically manifest. A truly definitive, incontrovertible diagnosis can only be achieved with a specific polymerase chain reaction test or, in exceedingly rare and extreme cases, a direct brain biopsy.

Cerebrospinal fluid analysis remains the most accessible diagnostic pillar. Ninety percent of patients will exhibit abnormal cerebrospinal fluid. In the initial, hyper-acute phase of the infection, polymorphonuclear leukocytes may predominate, but this rapidly changes to a state of profound lymphocytosis. The total cell count typically varies between 10 and 1000 cells/mm^3. In acute conditions, red blood cells may be found in the fluid, accompanied by xanthochromia due to microscopic hemorrhagic necrosis. Protein levels in the fluid frequently increase by 50 to 200 mg/dL, while glucose levels generally remain normal or are slightly decreased. However, clinicians must be acutely aware that the initial cerebrospinal fluid profile can be completely normal in approximately 5 to 10 percent of patients, particularly in children.[16]

A critical teaching point derived from this case report is the inherent unreliability of early computed tomography imaging. While specific research indicates that computed tomography scans show a typical image in 50 to 75 percent of cases—specifically, a hypodense area in the temporal or frontal lobe that can extend to the occipital lobe caused by brain tissue necrosis and edema—this typical image classically does not appear until after the first week of the illness. Therefore, obtaining an initial normal computed tomography scan in a deeply comatose pediatric patient, as seen in our case, perfectly aligns with the temporal limitations of this imaging modality in the acute phase of the infection and must never be used to rule out the disease. Advanced studies confirm that magnetic resonance imaging examinations are vastly more sensitive and consistently show positive pathological results much earlier than computed tomography scans. Furthermore, the use of single photon emission computed tomography can show distinct areas of severe hypoperfusion in the temporal or frontal lobe in the very early phase of the disease. However, due to severe logistical and financial constraints, neither magnetic resonance imaging nor single photon emission computed tomography was available or performed for the patient in this report.

The global medical literature has extensively published reports on gold-standard diagnostic methods, primarily advocating for the widespread use of polymerase chain reaction, which typically produces positive results much earlier than relying on serum antibody titers.[17] Polymerase chain reaction testing boasts a highly impressive sensitivity of 94 to 98 percent and a specificity of 98 to 100 percent. This specific test typically becomes positive within 24 hours of symptom onset and importantly, remains detectable for 5 to 7 days, even after the initiation of aggressive acyclovir therapy. Other definitive gold-standard tests include direct brain biopsy and subsequent virus isolation directly from the harvested brain tissue. Unfortunately, in many regions of Indonesia and other developing nations, laboratory facilities remain very limited, and the financial cost associated with advanced molecular testing is prohibitively high, making absolute confirmation with the gold-standard diagnosis exceedingly difficult, if not impossible.

Because a definitive way to confirm the diagnosis in the early phase is often absent, a high index of suspicion, rapid clinical diagnosis, and the prompt initiation of antiviral therapy while awaiting any available confirmation are absolutely crucial for patient survival.[18] Symptomatic and supportive treatment is functionally similar to that for other types of encephalitis; it includes the aggressive management of seizures, the reduction of life-threatening brain edema and increased intracranial pressure, the control of hyperpyrexia, the management of

respiratory distress, and the prevention of secondary nosocomial infections. The primary and most consequential difference is that highly specific, targeted antivirals can and must be administered.

Antiviral treatment must be initiated as early as possible to prevent irreversible, catastrophic hemorrhagic necrosis, which typically becomes firmly established exactly four days after the onset of the encephalitis. The universally accepted standard of practice is to promptly and aggressively treat any patient suspected of having the disease—presenting with the classic triad of fever, seizures, decreased level of consciousness, and potential hemiparesis—and then make a clinical decision to continue or discontinue the treatment based on eventual laboratory confirmation or the patient's clinical trajectory.[19]

Intravenous acyclovir has been conclusively shown in numerous large-scale clinical trials to be vastly superior to older medications like vidarabine, solidifying its place as the definitive drug of first choice. The standard pediatric dosing regimen is 30 mg/kg/24 hours, meticulously divided into three equal doses. In several modern pharmacological studies, the recommended dose is aggressively increased to 45 mg/kg per day in three divided doses for children, and up to 60 mg/kg per day in three divided doses for neonates, with the therapy continuing for up to 21 uninterrupted days to prevent viral relapse. To prevent serious nephrotoxicity, the medication must be administered slowly using a precise syringe pump or further diluted to a volume of 100 ml in a 5 percent glucose solution and administered over a period of 1 hour. The primary dose-limiting side effects include a significant increase in serum urea and creatinine levels, which are entirely dependent on the drug's peak plasma concentration. Diligent, slow administration of the drug combined with adequate intravenous hydration will effectively reduce the incidence of these renal side effects.

The concurrent use of adjuvant corticosteroids in the management of this specific viral encephalitis remains a subject of intense and ongoing controversy within the medical community. The potential clinical benefit of corticosteroids lies in their powerful ability to suppress the overwhelming, immune-mediated inflammatory damage and subsequent cerebral edema. However, this benefit is highly questionable due to their inherent potential to simultaneously enhance and accelerate viral replication by inducing a state of systemic immune suppression. Consequently, many prominent clinical investigators strictly recommend using corticosteroids exclusively for patients demonstrating clear evidence of significant, life-threatening cerebral edema and a rapidly expanding mass effect. Despite these concerns, a notable nonrandomized clinical trial demonstrated a clear survival and functional benefit in the corticosteroid treatment group when evaluated at a three-month follow-up interval.

One of the most reliable clinical indicators of successful antiviral therapy is the rapid and sustained recovery of consciousness, typically occurring within just 1 to 3 days of drug initiation, after which the patient has a vastly improved chance of living without severe, debilitating residual symptoms. All of these initial clinical manifestations are frustratingly atypical and difficult to distinguish accurately from encephalitis caused by other, less destructive viruses. However, patients who present to the emergency department already in a deep coma carry a very poor prognostic factor; these patients tragically often die or only recover while burdened with severe, permanent residual neurological symptoms. In fatal cases, death usually occurs rapidly within the first two weeks of the illness.[20]

The primary limitation of this case study is the inescapable lack of advanced molecular confirmation via polymerase chain reaction testing, and the inability to utilize magnetic resonance imaging to definitively map the exact neuroanatomical extent of the viral involvement. Furthermore, the absence of electrophysiological monitoring limits the ability to map subclinical seizure activity. While the diagnosis remains technically presumptive based strictly on the exceptional therapeutic response to specific antivirals

and the correlating clinical trajectory, the evidence is overwhelmingly supportive of the diagnosis. Future global health research and international funding initiatives must urgently prioritize the development, validation, and widespread dissemination of rapid, highly cost-effective, point-of-care molecular diagnostic assays for neurotropic viruses. This is essential to ensure equitable diagnostic capabilities and improve survival outcomes in resource-limited medical settings across the globe.

4. Conclusion

A severe case of herpes simplex encephalitis was successfully managed and reported in a 4-year-old girl. The diagnosis was established through meticulous evaluation of the patient's medical history, detailed physical examination, and fundamental laboratory tests, all of which indicated the presence of the disease. Despite the absolute lack of gold-standard diagnostic tools—such as molecular polymerase chain reaction assays, brain biopsy, and specialized neuro-monitoring—a rapid and decisive commitment to empirical symptomatic and supportive therapy, tightly coupled with the immediate administration of specific intravenous acyclovir, led to a profound and life-saving clinical improvement. This case unequivocally demonstrates that in resource-constrained environments, a high index of clinical suspicion must drive immediate empirical antiviral intervention, which remains the single most critical action to prevent catastrophic neurological morbidity and secure patient survival.

5. References

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