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Herpes simplex virus encephalitis: A literature review

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ABSTRACT

HSVE (Herpes simplex virus encephalitis) is an infection caused by herpes simplex virus type 1 (HSV-1) or type 2 that produces neurologic problems. HSVE is associated with significant morbidity and mortality in adults even with antiviral medication, and it is a fatal disease in babies and children regardless of treatment. The most likely pathways include retrograde transmission through the olfactory or trigeminal nerves, as well as hematogenous spread. The most common presenting symptoms are encephalopathy, fever, convulsions, headache, and regional neurologic dysfunction. An accurate history and physical examination are required to identify Herpes simplex virus encephalitis (HSVE), and a prompt assessment is advised after the diagnosis has been established. HSVE is a neurodegenerative disease that may be fatal. Rapid diagnostic work-up and early diagnosis in all suspected or confirmed cases will result in early initiation of intravenous acyclovir, which may decrease morbidity and death.

Keywords: herpes simplex virus, encephalitis, brain parenchyma, morbidity and mortality

INTRODUCTION

Encephalitis is an inflammation of the brain parenchyma that causes neurological impairments. It can be caused by infection, post-infectious infection, or non-infectious infection. The disease is the most prevalent etiology of encephalitis, accounting for almost half of all cases (1).

Herpes simplex virus encephalitis (HSVE) is a herpes simplex virus type 1 (HSV-1) or type 2 infection that produces localized or extensive neurologic problems (HSV-2). Herpes simplex virus encephalitis is caused by HSV-1 in the vast majority of cases, with HSV-2 accounting for fewer than 10% of cases, particularly in immunocompromised individuals (2). Each year, HSV-1 encephalitis affects 10% to 20% of the 20,000 viral encephalitis cases in the United States. The worldwide incidence is thought to be between 2 and 4 per 1,000,000 individuals (3).

Herpes simplex 1 (HSV-1) encephalitis is linked with significant morbidity and mortality in adults despite antiviral medication, and it is a fatal disease in babies and children regardless of treatment (4). We reviewed the etiology, pathophysiology, clinical manifestations, diagnosis, management, and prognosis of herpes simplex virus encephalitis-1 (HSV-1)/herpes simplex virus encephalitis (HSVE).

ETIOLOGY

HSV-1 and HSV-2 are human herpesvirus families that include varicella-zoster virus (VZV; HHV-3), Epstein-Barr virus (HHV4), cytomegalovirus (HHV-5), HHV-6, HHV-7, and HHV-8 (herpesvirus linked with Kaposi's sarcoma). Herpes simplex virus, mainly HSV-1, is the most common cause of herpetic encephalitis (5).

The herpes virus has a four-layered structure that is unique. An icosapentahedral capsid made up of capsomeres surrounds a core carrying a huge double-stranded DNA genome, which is encircled by a layer of amorphous protein called the tegu-

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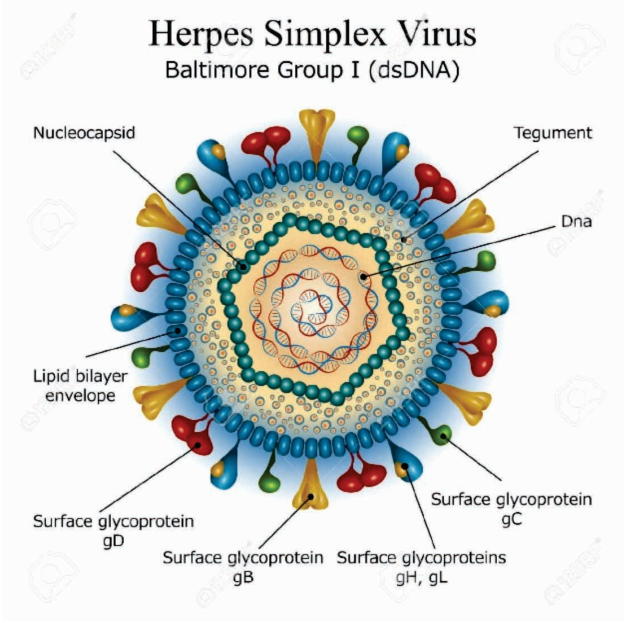


FIGURE 1. Herpes simplex virus morphology (5)

ment. The outermost layer is encased in a glycoprotein-rich lipid bilayer sheath (Figure 1) (6).

The likelihood of herpes virus infection is enhanced when the toll-like receptors-3 (TLR-3) pathway is disturbed, changes in the MHC class 1 allotype, and the high-affinity receptor/ligand combination KIR2DL2/HLA-C1 and CD16A-158V/dimorphism are present. Immunosuppressive medications (e.g., natalizumab) and anti-inflammatory therapies (e.g., TNF alpha-blockers) were shown to increase HSV-1 encephalitis susceptibility (3).

PATHOPHYSIOLOGY

HSV affects the human central nervous system (CNS) in an unknown manner. The most probable pathways are retrograde transmission through the olfactory or trigeminal nerves (Fig. 2) or hematogenous spread. On the other hand, the prevalence of infectious viral lesions in the orbitofrontal and mesiotemporal lobes indicates that hematogenous distance is rare. Experimental results in animals show that virions may travel to the contralateral temporal lobe through the anterior commissure, supporting the idea of transmission to the CNS by one or both of the trigeminal and olfactory channels (7).

Both the virus and the host's immunological factors influence the pathogenicity of a virus. The exact mechanism of nerve injury is unclear. It may happen as a direct consequence of the virus or as a result of the infection's inflammatory reaction. Pre-acyclovir research showed a rapidly growing viral infection in the limbic system that spreads over both sides of the hemisphere in three weeks, causing inflammation and necrosis in the problematic regions (8).

Lytic and hemorrhagic processes asymmetrically distributed throughout the medial temporal and inferior frontal lobes rapidly destroy neurons. Wasay et al. found that 60 percent of patients had temporal lobe involvement, 55 percent of patients had temporal and extratemporal disease, and 15 percent of patients had only extratemporal pathology. In the medial temporal lobes and inferiorly in the frontal lobes, lytic and hemorrhagic regions are

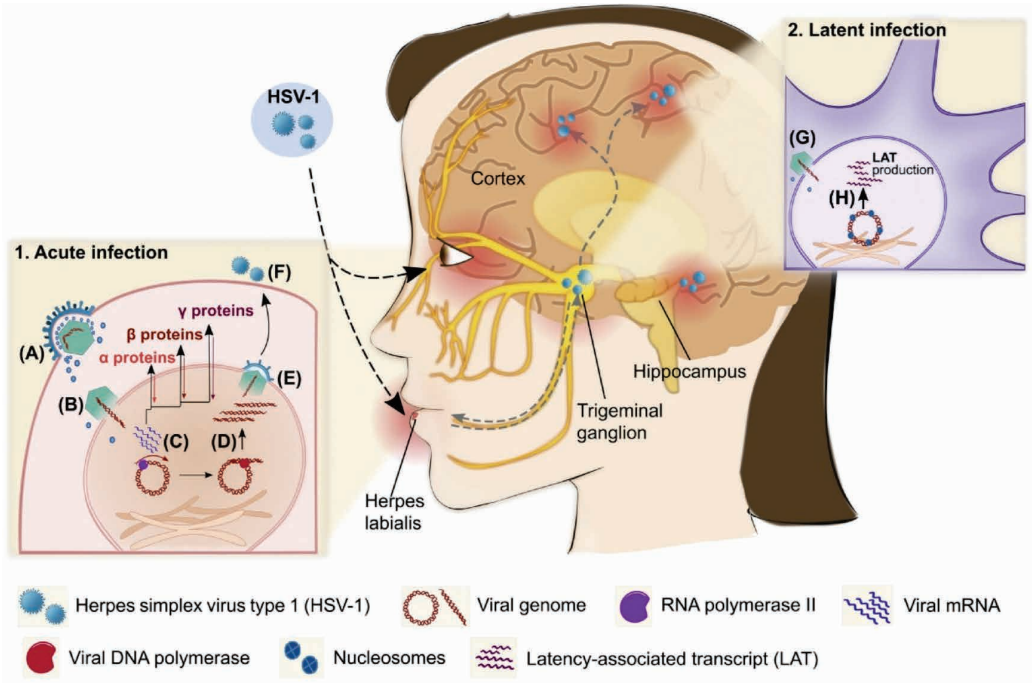


FIGURE 2. Pathophysiology of herpes simplex virus encephalitis (10)

common. Hemorrhagic encephalitis in orbitofrontal or limbic tissues is a pathognomonic finding on brain biopsy. There are also Cowdry A inclusion bodies. There have also been reports of focal corticosteroid-responsive granulomatous pathology (9).

The frontal and mesiotemporal lobes, as well as the limbic system, are all connected via the olfactory nerve, which does not travel through the thalamus. The trigeminal nerve, which may also extend to the orbitofrontal and mesiotemporal lobes, innervates the meninges. Because the sensory nucleus of the trigeminal nerve is situated in the brainstem, brainstem encephalitis associated with HSVE becomes more frequent if this is the primary route of infection into the CNS (11).

Although the incidence of HSVE is not increased in immunocompromised individuals, their symptoms may be subacute or atypical (12). The inflammatory cascade, which includes primed innate and adaptive immune cells, causes necrosis and death in infected cells. The inflammatory reaction, especially leukocyte aggregation, is critical for virus control, as is the host immunological response, which may cause tissue damage and neurologic complications (13).

The virus establishes a persistent latent state in the host after initial infection, which remains dormant until awakened. Several complicated processes must be balanced in order to sustain delay. Among them include viral lytic phase gene inhibition, abrogation of host cellular defense mechanisms (e.g., apoptosis), and evasion of host immunity, including innate and acquired immunological responses (e.g., suppression of expression of major histocompatibility complexes). In the trigeminal ganglia, HSV-specific CD8+ T lymphocytes play a role in keeping the virus latent. Viruses that have been reactivated may infect adjacent neurons and spread to organs innervated by infected dorsal root ganglia, resulting in recurring sickness and the release of infectious viral particles that can infect others (14).

CLINICAL MANIFESTATIONS

Some patients experience prodromal symptoms such as upper respiratory symptoms or other systemic illnesses. Encephalitis symptoms develop many days later. Encephalopathy, fever, seizures, headache, and localized neurologic impairment are the most prevalent presenting signs (15). According to the location of the most prevalent lesions in the temporal lobe, seizures are a common symptom of herpetic encephalitis. Seizures (32%), aberrant behavior (23%), decreased awareness (13%), and disorientation (13%) were the most common reasons people went to the hospital in 106 cases with HSVE (16). According to Sellner et al., the most frequent kind of seizure in herpetic encephalitis was focal seizures (65%), followed by generalized seizures (23%), and a mix of the two (12%) (17).

Recognizing the encephalitis symptoms, which includes changes in mental status (> 24 hours) and inflammation of the brain parenchyma, such as fever, seizures, and localized neurological impairments, is critical for early diagnosis and treatment of HSV encephalitis. Behavioral or personality changes are frequently mistaken as psychiatric disorders. In HIV-positive patients, HSV-1 encephalitis can occasionally develop as recurrent brainstem encephalitis, with symptoms such as aphasia and intracerebral hemorrhage (3).

The most common physical symptoms are fever and mental problems. The neurologic ailment typically arises out of nowhere and lasts for less than a week. Symptoms include cranial nerve palsies, hemiparesis, aphasia, ataxia, visual field abnormalities, and papilledema (15).

DIAGNOSTIC

Without postponing therapy, the evaluation should be completed as quickly as possible. Suspicion should be raised, especially in patients who have a fever and have a damaged immune system. Misdiagnosis as a psychiatric disorder can occur due to cognitive, behavioral, or personality abnormalities. In order to diagnose herpes encephalitis, a thorough medical history and physical examination are required. Anamnesis is all about looking for possible causes of encephalitis, such as immunosuppressive medicines, immunocompromised disease, travel history (near or far), mosquito bites, or flea bites. Weight loss, infection symptoms like fever and rash, and neurological or psychiatric issues like aphasia, behavioral abnormalities, and seizures should all be investigated (18).

The diagnosis might be guided by a thorough physical and neurological examination. The presence of cranial nerve issues indicates brainstem encephalitis, hence the pattern of neurological abnormalities might help restrict the differential diagnosis. Movement abnormalities, tremors, and symptoms of basal ganglia diseases could all be signs of something more serious. It's especially difficult to distinguish encephalitis in the elderly and immunocompromised patients. Herpes encephalitis can be diagnosed with laboratory tests and early neuroimaging (18).

Routine blood tests may show indications of infection or identify kidney issues, requiring a dose adjustment. Focused neurologic deficits, computed tomography (CT) or magnetic resonance imaging (MRI) abnormalities, and CSF fluid imaging may

take time to reveal a problem. Only the HSV polymerase chain reaction (PCR) test or a rarely performed brain biopsy may give a definite diagnosis.

Laboratory findings

The following tests were performed: complete blood count with differential count, electrolytes, kidney and liver function, blood culture, HIV test, and treponemal test. Blood testing for *Mycobacterium tuberculosis* should be considered in immunocompromised individuals at high risk of TB (19).

Lumbar spine puncture

In instances of encephalitis, a lumbar puncture may be a useful additional test that offers a wealth of information. If there are no contraindications, a lumbar puncture should be done. The CSF fluid extracted is about 10 milliliters. The criteria that were examined were opening pressure, cell quantity and ratio, protein, glucose, Gram stain, KOH, IgG index, bacterial culture, HSV-1/HSV-2 PCR, VZV PCR, enterovirus PCR, TB PCR, Indian ink, and cryptococcal antigen (Table 1). Herpetic encephalitis is characterized by normal or slightly greater opening pressure, significant pleocytosis (>5 nucleated cells/ml or 10-200/mm3), increased erythrocytes (10-500 U/l), moderately raised protein (50-100 mg/dl), and normal or reduced glucose (30-40 mg/dl) (16,20).

TABLE 1. Cerebrospinal fluid (CSS) parameters measured

Parameters	Hasil
Opening pressure	Normal or slightly increased
Cell	Pleocytosis (>5 nucleated cell/ml or 10-200/mm^3)
Erythrocyte	Increased (10-500/µl)
Protein	Slightly increased (50-100mg/dl)
Glucose	Normal or decreased (30-40 mg/dl)

Polymerase chain reaction (PCR)

CSS sells polymerase chain reaction (PCR) kits for HSV-1 and HSV-2. The PCR test has a high sensitivity (96%) and specificity (98%) rate. It may test positive as soon as 24 hours after the beginning of symptoms and remain positive for at least 5-7 days after starting antiviral treatment. Early in the course of the illness, false-negative findings may occur. In patients with clinically relevant encephalitis, acyclovir is still administered on a trial basis, and CSF PCR HSV testing is repeated within 3-7 days (21,22).

Serology

Serological testing of blood or CSF may be useful for evaluation, but it plays no role in the patient's diagnosis or immediate treatment. The ratio of antibody levels in blood and cerebrospinal fluid, as well as high antibody levels, are not therapeutically helpful (3).

Computerized tomography (CT) scan

In most cases, CT scanning is used as the initial neuroimaging test in encephalopathy patients. Edema, a midline shift of the brain, a mass that requires prompt action, or a contraindication to lumbar puncture may all be seen by a CT scan. Hypodense lesions (often in the temporal lobe or frontal lobe) after 3-4 days, edema, and increasing contrast enhancement after one week are seen in 25-80 percent of HSVE patients. CT scans can't tell if a disease is caused by a virus or anything else, and they're less sensitive early on. MRI is superior to CT Scan in terms of diagnosis. In one study, CT scans revealed abnormalities in half of the instances, while MRI revealed abnormalities in nearly all of the cases (16).

Magnetic field resonance MRI with or without contrast is the neuroimaging of choice for detecting encephalitis and abnormalities in most instances of herpes encephalitis. A brain MRI is the most sensitive and specific diagnostic for HSVE, particularly early on in the disease's course. Asymmetric hyperintense lesions with edema may be observed on MRI in the mesiotemporal, orbitofrontal, and insular cortex (23).

In numerous studies, diffusion restricted DWI was discovered early in HSVE and was the initial radiological symptom (24). Diffusion confined in the front temporal lobe and insular cortex was identified in HSVE patients with negative PCR results. DWI has a higher sensitivity than FLAIR. According to several studies, DWI has more lesions early in the illness course (less than 2 weeks) than FLAIR. In the later phases of the disease, FLAIR will display anomalies. The thalamus showed changes or lesions in FLAIR but not in DWI (25). Changes or lesions in the unilateral or frontal temporal lobe on DWI, along with suitable clinical characteristics, should be considered diagnostic clues for viral herpes encephalitis (26).

Electroencephalography (EEG)

Electroencephalography (EEG) has an 84 percent sensitivity to abnormal patterns in HSVE. During the first 5-7 days of illness, you may notice focal abnormalities (spike and slow- or periodic sharp-wave patterns in the temporal lobe) or widespread slowness. A periodic complex and periodic lateralized epileptiform discharge (PLED) of approximately 2-3 Hz originating from the temporal lobe, as well as sufficient clinical presentation, are indicative of HSVE. On the other hand, Benető et al. discovered nine individuals with HSVE but no PLED activity or other EEG abnormalities. PLED is not specific for HSVE and may be absent early in the course of the disease, but it does aid in diagnosis (27).

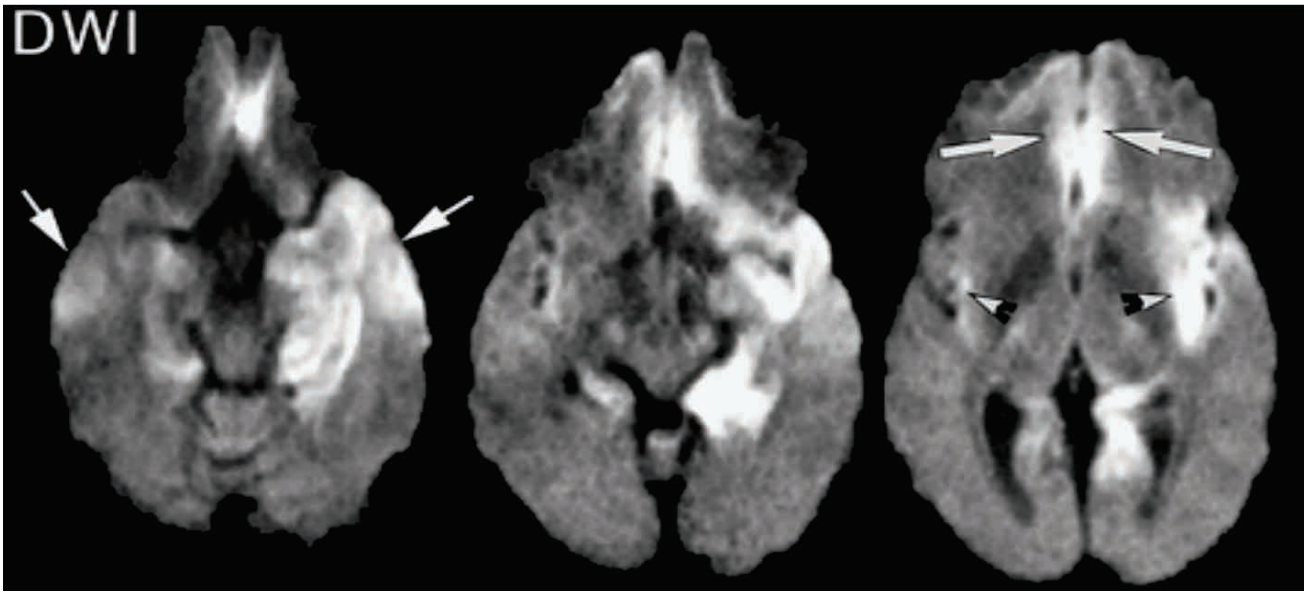


FIGURE 3. DW MR image (6,000/108) showing bilateral restricted diffusion in the temporal lobe (short arrow), inferior frontal lobe (long arrow), and insula (arrowhead), which is the typical distribution for herpetic encephalitis

Periodic sharp-wave patterns may emerge on days 2-15 of the illness course, even before abnormalities on a head CT scan. Sutter et al. discovered 12 individuals with herpes encephalitis among 103 patients with encephalitis between 1997 and 2011 (28). Patients with herpetic encephalitis exhibit an EEG pattern with periodic discharge and localized slowing in the frontotemporal and occipital regions, which is different from other etiologies of encephalitis. These results are consistent with previous studies. Typical EEG abnormalities in individuals with herpetic encephalitis (periodic sharp-wave patterns and periodic lateralized epileptiform discharges (PLEDs)) are shown in Figure 4.

Brain biopsy

Brain biopsies have been less common in recent years because to the availability of the HSV PCR test in CSS, which is very sensitive and specific. A total of 3% of those who underwent brain biopsies developed problems as a consequence of the surgery. Antiviral medications on the market now have a good safety record. In suspected cases, empiric intravenous acyclovir therapy may be started for at least a short period of time before the diagnosis is established. Only a brain biopsy revealed a rare incidence of corticosteroid-responsive vasocentric granulomatous inflammation in two adult individuals with HSV-1 encephalitis. The patient exhibited temporal lobe MRI abnormalities, positive intrathecal IgG antibodies in matched blood and CSF, but no CSF PCR. A contemporary option for brain biopsy is undiagnosed encephalitis despite extensive testing, in which the patient's condition does not improve or worsens (8).

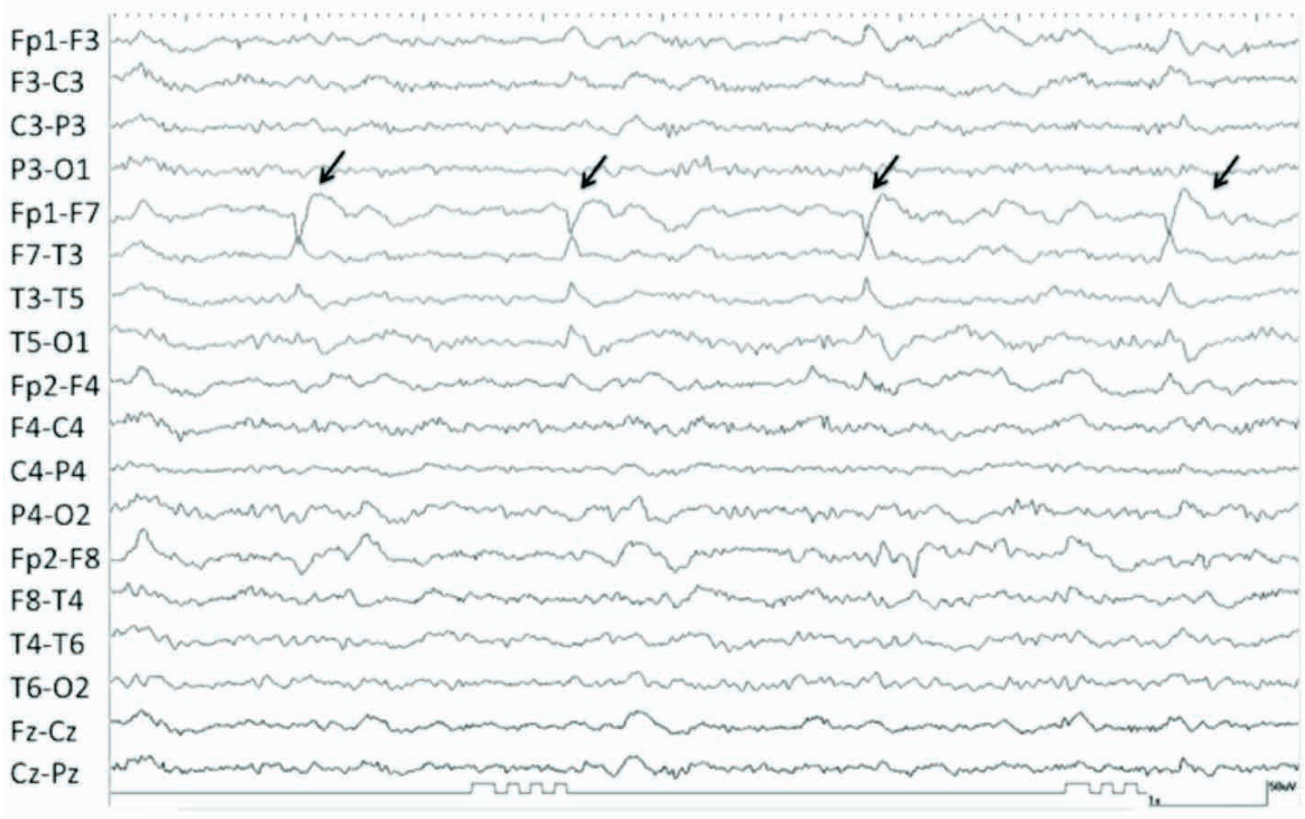
DIFFERENTIAL DIAGNOSIS

Herpes simplex virus encephalitis is difficult to diagnose. According to a study, 43% of 251 cases of temporal lobe encephalitis were caused by an infectious process, with the herpes simplex virus being the most frequent. Herpes encephalitis can be caused by a variety of infectious agents, autoimmune disorders, and other diseases (Table 2) (26).

TABLE 2. Some diseases that resemble herpetic encephalitis

Vascular	Ischemic stroke Subarachnoid hemorrhage Intracerebral hemorrhage Cerebral venous sinus thrombosis Posterior reversible encephalopathy syndrome Reversible vasoconstriction syndrome
Vasculitis	Metabolic derangement Hepatic and/or renal encephalopathy Hypoglycemia, hyponatremia Septic encephalopathy Mitochondrial encephalopathy Wernicke's encephalopathy
Toxic	Alcohol, drugs
Trauma	Head trauma
Neoplastic	Primary brain tumor Metastases
Epileptic	Nonconvulsive status epilepticus

The differential diagnosis should include conditions that may resemble encephalopathy or encephalitis, such as infections of the CNS caused by bacteria, such as mycobacteria, atypical organisms, viruses, prions, fungi, or parasites, septic encephalopathy and hypoxemic encephalopathy are two types of encephalopathy, infectious and non-infectious causes of encephalitis (e.g., autoimmune or



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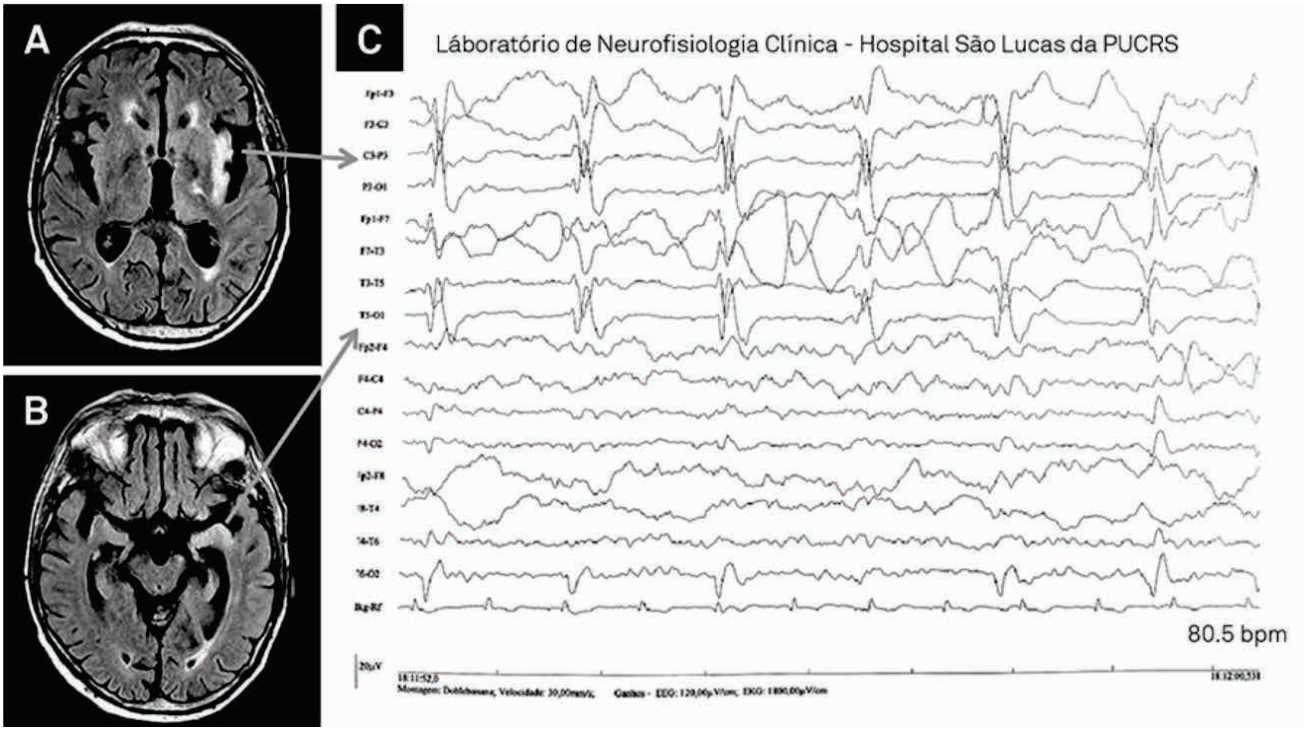

b

FIGURE 4. EEG features of periodic sharp-wave (a) and periodic lateralized epileptiform discharges (PLEDs) in a patient with herpetic encephalitis (29)

paraneoplastic encephalitis, acute disseminated encephalomyelitis), metabolic causes include hepatic/uremic encephalopathy, Wernicke's encephalopathy, mitochondrial encephalopathy, hypoglycemia, hyponatremia, hypernatremia, hypocalcemia, and hypercalcemia, alcohol and heavy metals, cerebro-

vascular accidents, primary or secondary brain tumors, seizure disorders, vasculitis, neurosyphilis, SLE, Behcet's disease, and trauma (3).

In the differential diagnosis of viral encephalitis, arboviral infections such as West Nile and St. Louis encephalitides, Eastern and Western horse encephalitides, and California and Japanese encephalitides should be considered. Mumps, enterovirus, dengue fever, adenovirus, lymphocytic choriomeningitis, hypermutated measles virus-induced subacute sclerosing panencephalitis, and progressive multifocal leukoencephalopathy caused by the JC virus are some of the other etiologies (3). The diagnostic criteria for encephalitis were divided into major and minor categories (Table 3).

TABLE 3. Criteria for the diagnosis of encephalitis

Major criteria (must have)	Subacute onset of loss of consciousness, memory, mental status, or new onset of unexplained psychiatric symptoms
Minor criteria (at least 2 of the following symptoms for the diagnosis of encephalitis)	1. Fever > 38°C within 72 hours before or after the onset of prodromal symptoms 2. Seizures (focal or generalized) that are not related to previous seizures 3. Pleiocytosis (WBC > 5/mm3) on CSF examination 4. The presence of inflammation of the brain parenchyma on neuroimaging examination (acute or subacute)

There are a few things to think about when it comes to the cause of undiagnosed herpetic encephalitis.

1. Failure to detect the symptoms of encephalitis. Inadequate supporting investigations, such as the lack of CT Scan/MRI facilities and CSF examinations that can help diagnose encephalitis, can cause it (30).
2. CSF pleocytosis is less common in immunocompromised patients, making diagnosis more difficult (30).
3. PCR tests that provide erroneous negative results. False negatives may occur with HSV-1 PCR, particularly in children and early in the course of HSVE. Patients should be treated empirically if suspicion is high, even if the PCR is negative, and the HSV PCR of the CSF should be done within 3-7 days (21).

TREATMENT

To diagnose herpes simplex virus encephalitis (HSVE), an accurate history and physical examination are essential, and quick evaluation is recommended after the diagnosis has been made. Consider HSVE in a febrile patient with CSF encephalopathy and pleocytosis if no other cause can be found. In individuals suspected of having HSVE, start empiric acyclovir therapy very away. since acyclovir is the treatment of choice, is reasonably safe, and the prognosis for untreated HSVE is lacking pending confirmation of the diagnosis (31). The first responsibility is to recognize and respond to emerging emergencies. Figure 5 depicts the flow of diagnosis and treatment.

It is impossible to overestimate the value of a hemodynamic and airway evaluation. Seizures and high intracranial pressure (ICP) should be watched closely. Other encephalopathy causes, such as hypoglycemia, hypercarbia, electrolyte imbalances, and so on, may be examined and treated promptly in an emergency. Patients should be properly prioritized and admitted to the critical care unit after initial stabilization (ICU). A reduced level of awareness, significant comorbidities, and autonomic dysfunction are all signs of ICU admission (32).

Simple methods (e.g., raising the head of the bed, diuresis with medications like furosemide) to more elaborate procedures (e.g., mannitol and steroids, intubation with hyperventilation) are used to treat cerebral edema (32).

Seizures are a common symptom of HSVE, and its behavioral symptoms may resemble seizures. Anticonvulsant therapy may be used if episodes are frequent or if electroencephalography (EEG) indicates signs of nonconvulsive attacks. Although benzodiazepines do not prevent subsequent seizures, they can be used to treat status epilepticus (32).

Anticonvulsant treatment

Recurrent seizures, also known as status epilepticus, require a proactive therapeutic and diagnostic strategy. It is suggested that intravenous benzodiazepines and anticonvulsants be used. There are no studies in HSVE that compare the effectiveness of various first- and second-line antiepileptic medicines. Seizures in people with HSVE are treated in the same way as seizures in people with generalized secondary focal or generalized epilepsy are treated (17).

The antiepileptic medicine was maintained using oral forms after the seizures were under control. The effectiveness of first- and second-line antiepileptic drugs, as well as the optimal length of antiepileptic treatment, were not discovered. Oral antiepileptic treatment is maintained for 6 to 12 months before progressively tapering down. When phenytoin or valproic acid are prohibited, such as during pregnancy, levetiracetam or lacosamide may be used instead. Despite this, their effectiveness and safety in the treatment of herpes encephalitis have not been extensively studied. Seizures were managed by low-dose lamotrigine and benzodiazepines in a number of instances of herpetic encephalitis during pregnancy (17).

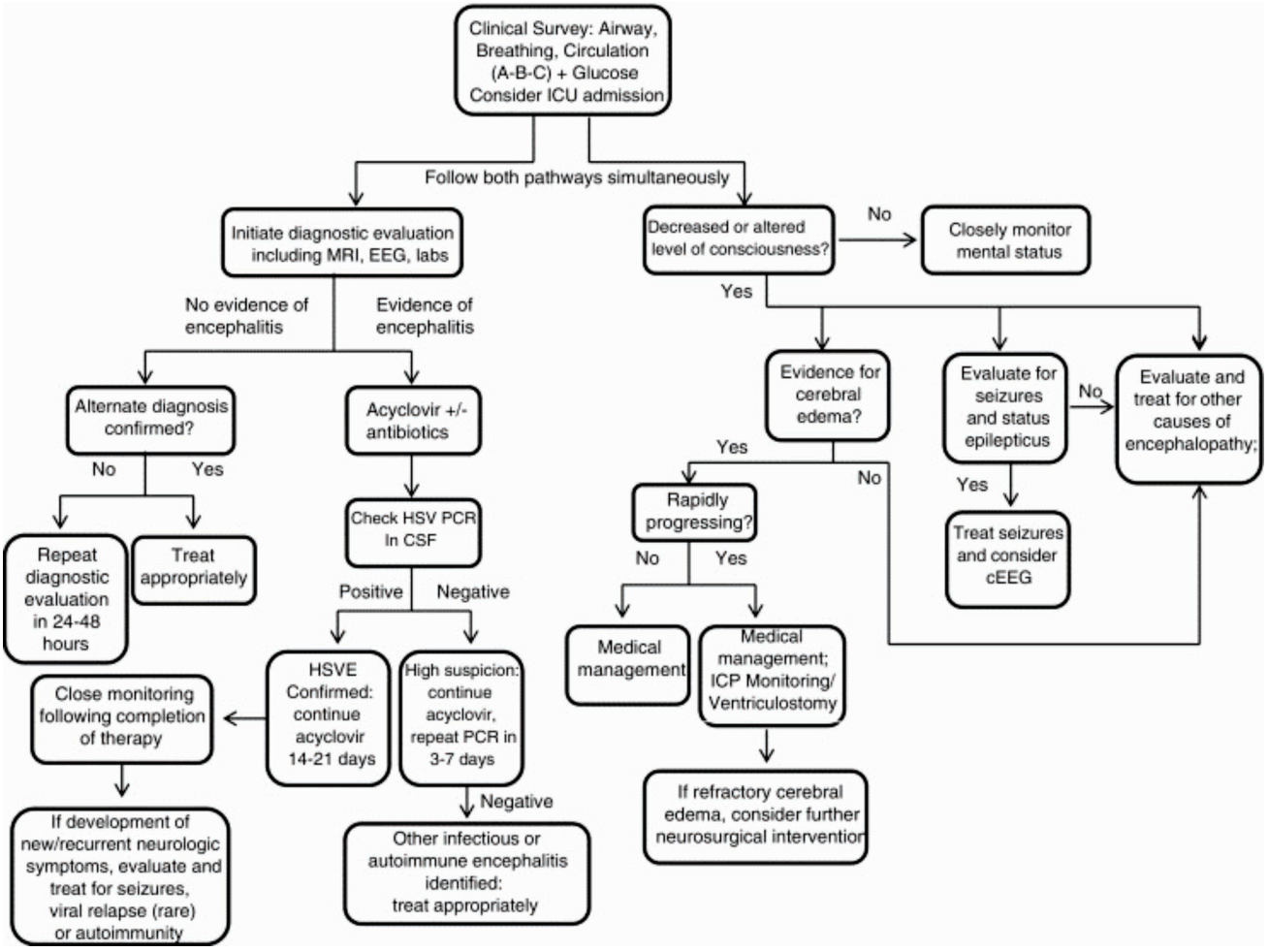

FIGURE 5. Treatment of a patient with encephalitis caused by the herpes simplex virus type 1 (HSVE). cEEG is for continuous electroencephalography, and CSF stands for cerebrospinal fluid. ICP stands for intracranial pressure, and ICU stands for intensive care unit. PCR stands for polymerase chain reaction, and SE stands for status epilepticus (32)

Antiviral treatment

Intravenous acyclovir at a dosage of 10 mg per kg of body weight every 8 hours is the most effective therapy for HSVE. Greater dosages (15-20 mg per kilogram of body weight) are given to children under the age of 11 and infants (3,33). Current recommendations recommend intravenous acyclovir for 14-21 days in HSVE patients. Despite the fact that acyclovir was only administered for 10 days in the original study, there have been few reports of recurrence, prompting most physicians to recommend a longer treatment period (mainly, many cases of degeneration appear to be immune-mediated rather than infectious). If the PCR is positive, many studies suggest repeating the CSF test on days 14-21, as well as a longer treatment period (34). According to UK guidelines for the treatment of encephalitis, acyclovir may be discontinued after another diagnosis is confirmed, or if HSV PCR of CSF is negative on two occasions for at least 24-48 hours, or if all of the following criteria are met: a CSF PCR result obtained more than 72 hours after the start of symptoms is negative; there hasn't been any change in awareness; the MRI of the brain is normal, and the number of leukocytes in the CSF is fewer than 5 per ml (18).

A delay in starting acyclovir for more than 48 hours is one of the features related to poor results. Viral and stem cell enzymes convert acyclovir to acyclovir triphosphate, which is a potent inhibitor of HSV DNA polymerase and therefore limits viral replication. Acyclovir is a reasonably safe medication with few severe side effects, such as thrombophlebitis and, in rare instances, crystal-induced nephropathy. Nephropathy may be caused by IV infusions, rapid administration, dehydration, concomitant use of nephrotoxic medicines, higher dosages, and underlying renal impairment. It's important to drink plenty of water when taking acyclovir. Immunocompromised individuals are more prone than immunocompetent persons to acquire acyclovir resistance. Routine use of oral valaciclovir for three months following the first dose of IV acyclovir showed no further cognitive improvement in HSVE patients when evaluated 12 months after the initial dose of IV acyclovir (35).

Acyclovir is classified as pregnancy category B by the US Food and Drug Administration, which means it presents no danger to humans. In 1,804 pregnancies, at least one large observational research showed no connection between first-trimester acyclovir, valaciclovir, or famciclovir exposure and a greater prevalence of congenital defects (36).

Corticosteroids

Corticosteroids in the treatment of HSVE are currently debatable. Corticosteroids have anti-inflammatory properties, but they also have the potential to promote virus multiplication due to immune suppression. Only those with substantial edema with mass impact should take corticosteroids (3).

In individuals with severe HSVE, steroids are utilized to alleviate cerebral edema (37). In one non-randomized retrospective human investigation, patients with HSVE who were given steroids other than acyclovir were compared to those who were given acyclovir alone. At three months, the steroid group had higher yields (38).

PROGNOSIS

Individuals with untreated HSVE have a 70% death rate, whereas 97% of healed patients still have problems (39). If not treated, HSVE will develop and may be deadly within 7-14 days if left untreated. Whitley et al. presented a landmark study that found 70% mortality in untreated patients and significant brain abnormalities in the majority of survivors (33).

The age and neurologic state of patients at the time of diagnosis influence their post-encephalitis prognosis. Patients who are asleep at the time of diagnosis have a poor prognosis, regardless of age. The prognosis for non-comatose people varies according on their age, with those under 30 having a higher chance (40).

Relapse following HSVE has been reported in 5-26 percent of patients, with the majority of relapses occurring within the first three months after treatment completion and affecting children more often than adults. Regressions in previous studies may be due to inadequate treatment time rather than true HSVE relapses. The pathogenic processes present during a relapse are distinct from those present during the first infection. Serial investigations of inflammatory markers and HSV viral load in relapsed patients' CSF revealed elevated inflammatory markers but no detectable HSV during relapse (41,42).

CONCLUSIONS

Infection is the most frequent etiology of encephalitis, accounting for almost half of all cases. HSV-1 is the most common cause. Each year, HSV-1 encephalitis causes 10% to 20% of the 20,000 viral encephalitis cases in the United States. Herpes simplex virus encephalitis has a high incidence of morbidity and mortality, even when diagnosed and treated early.

HSVE is a neurodegenerative disease that may be fatal. In all suspected or confirmed cases, prompt diagnostic testing and diagnosis will result in the administration of intravenous acyclovir as soon as possible, reducing morbidity and mortality. All patients with HSVE, whether suspected or confirmed by radiography, CSF profile, or EEG features, should start intravenous acyclovir therapy immediately once.

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