

A review with comments on herpes simplex encephalitis in adults

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ABSTRACT

Herpes simplex encephalitis (HSE) can cause permanent injury to the brain parenchyma. As such, it is usually treated as a medical emergency for which correct immediate diagnosis and introduction of specific therapies are critical for survival and prognosis. Here, the authors review the current status of diagnosis and treatments and discuss unsolved issues surrounding therapeutic interventions. The authors also highlight the current expectations for future management of HSE.

INTRODUCTION

Herpes simplex encephalitis (HSE) is an acute infectious disease of the central nervous system (CNS) caused by herpes simplex virus (HSV). It typically occurs in the frontal and temporal lobes, causing hemorrhagic necrotic lesions of brain parenchyma. HSE is the most common cause of sporadic fatal viral encephalitis,^[1] accounts for almost 20% of all cases of encephalitis,^[2] and has an annual incidence of 1 in 250,000 to 500,000.^[3]

In immunocompetent adults, more than 90% of HSE cases are due to HSV-1,^[4] whereas HSV-2 is typically responsible for HSE in immunosuppressed individuals.^[5]

Unfortunately, this CNS disease is life-threatening, as it can also affect the brainstem preferentially or both hemispheres simultaneously^[6] in addition to the frontal and temporal lobes, causing a series of clinical features including cognitive impairment, personality changes, seizures, aphasia, and focal weakness.^[7,8]

HSE is associated with 70% mortality in untreated patients. In treated cases, there is also about 30% mortality and a high-incidence of severe and permanent neurological sequelae, such as memory impairment, personality and behavioral abnormalities, or seizures.^[9,10] Because of its high morbidity and mortality, it has become a global public health problem with a huge economic impact on the whole society.



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With the development of the diagnosis, and antiviral therapies, the management of patients with HSE has improved rapidly in recent years. However, acyclovir resistance and a better understanding of pathogens and pathogenesis also represent new challenges.

Here, we review the current status of diagnosis and therapies for HSE and discuss current controversies and expectations for the treatment of this disease.

DIAGNOSIS

Current status of diagnosis

HSE is a medical emergency and correct and immediate diagnosis is fundamental for the prognosis and therapeutic interventions. At patient's first presentation a meticulous medical history and a careful neurological examination are critical. Peripheral blood count and cellular morphology, such as lymphocytosis, are also helpful in differential diagnosis. Cerebrospinal fluid (CSF) typically shows a lymphocytosis of 10-200/mm³ (or more) and increased protein of 0.5-1.0 g/L or more.^[7] During the early stage of the disease, electroencephalography (EEG) with the evidence of spike and slow wave localization to the temporal lobe might suggest HSE, however, EEG has a sensitivity of approximately 60% and a specificity of 80%.^[11]

Virus isolation in cell culture, serological tests for specific antigen or antibody production and brain biopsy play a crucial role for the etiology and diagnosis of HSE. However, all have been now replaced by the detection of HSV using polymerase chain reaction (PCR) in the CSF, that shows a sensitivity of approximately 96%, and a specificity of approximately 99%.^[12]

Neuroimaging is also importance in suspected HSE cases. Magnetic resonance imaging (MRI) is more specific and sensitive than computed tomography (CT), because of its non-ionizing radiation, multiplanar imaging capability, improved contrast of soft tissue, and high anatomic resolution.^[13,14] Usually MRI shows the abnormalities characteristic of edema and/or enhancement in temporal and frontal lobes, the insular cortex, and the angular gyrus.^[15-17] Nowadays, the use of DWI and FLAIR imaging is strongly encouraged,^[18] as approximately 5% HSE patients show a normal MRI at presentation.^[19] However, it is worth noting that the sensitivity of a new CT post-processing tool based on frequency-selective nonlinear blending (best-contrast CT) seems to be equal to that of DWI and FLAIR, as suggested in a recent study.^[20]

Unresolved issues in diagnosis

PCR-based test in CSF has been established as a gold

standard method for the diagnosis of HSE. However, there is evidence of pseudo-negative result influenced by the time of CSF sample collection: the PCR may be negative for HSV-1 during the first 3 days of the illness,^[12] however, if the CSF is re-examined after a few days, the PCR may then become positive. The European consensus report^[21] recommends repeating the CSF PCR routinely after 14 days of treatment, although this does not guarantee a positive result at 10-14 days after illness. In particular, it has been previously shown that PCR positive result most commonly occurs during the first week of infection, even in the case of concurrent treatment with acyclovir.^[22] In light of these data, clinicians should give full consideration to the patient's clinical manifestations and curative effects to determine if the PCR test on CSF should be repeated.

THERAPY

Current status of therapy

Correct immediate introduction of specific therapies could reduce the extent of injury and impact on survival.

Antiviral therapy

Acyclovir (ACV), a guanosine analogue, targets viral DNA replication and is the most efficient drug for the treatment of HSE. The recommended dose is 10 mg/kg IV every 8 h for 14 days. In immunocompromised patients or children under 12 years, the treatment usually lasts for at least 21 days. Therapy should begin as soon as HSE is suspected, in fact treatment delays are usually associated with a significantly poorer disease outcome.^[3] Renal toxicity, caused by crystallization of ACV in the kidneys, can be prevented by hydration and slow infusion rates, however kidney function should be monitored and any sign of renal impairment should be considered.^[23]

Valacyclovir (VCV), an L-valyl ester prodrug of ACV, which is converted to ACV by the hepatic enzyme VCV hydrolase has been shown to have a better oral bioavailability than ACV. A recent study indicated that the administration of VCV at 1,000 mg three times daily result in adequate acyclovir concentrations in the CSF and could be considered an acceptable early treatment for suspected HSE in resource-limited settings.^[24]

Corticosteroids

Corticosteroids as an adjunct treatment for HSE are still controversial. One study showed that corticosteroids increase patient benefit^[25] but they are not routinely recommended^[3,16,26] as a large prospective randomised trial is still needed. However, steroid administration is recommended in situations where HSE patients show severe cerebral edema that could result in severe brain

swelling, coning and death and lumbar puncture is to be avoided.^[27]

Other therapies

Supporting therapies are also very important for HSE patients to prevent a variety of complications, such as respiration or cardiac failure, fluid balance disorders and deep vein thrombosis. For patients with increased intracranial pressure, neurointensive care unit management is essential. Clinicians in the UK recommended that the management of HSE should be a participatory process, which is co-produced by health professionals, patients, and their families.^[28]

Unresolved issues in therapy

One important issue to consider is whether it is safe to stop acyclovir when the CSF PCR result is negative. The 2012 ABN guidelines recommend that aciclovir might be stopped in immunocompetent patients, if: (a) an alternative diagnosis has been made, or (b) HSV PCR in the CSF is negative on two occasions in a 24-48 h period and MRI is not characteristic for HSV encephalitis, or (c) HSV PCR in the CSF is negative once after 72 h from neurological symptoms appearance, with unaltered consciousness, normal MRI (performed after 72 h from symptoms appearance) and with white cell count in the CSF less than $5 \times 10^6/L$ (B, III).^[3]

Another issue to take into account is that the combination of acyclovir with other antiherpetic drugs is either synergistic or additive. A randomized controlled study by The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group showed that, following standard treatment with intravenous ACV for PCR-confirmed HSE, an additional 3-month course of oral VCV therapy did not provide additional benefit.^[29]

Up to date, there is a common belief that no other drugs can replace ACV for the treatment of HSE and drug combinations are not recommended.

PROSPECTS

Although ACV treatment in HSE is very effective, patient mortality is still approximately 14-19% and 45-60% of the survivors suffer from neuropsychological sequelae.^[29] On the other hand, viral resistance is also a potential limitation of HSE therapy.

In this context, there is an urgent clinical need for new therapeutic methods which can result in better clinical outcomes for HSE patients and can prevent viral reactivation or infection. New approaches, such as TLR agonists,^[30] IL-1 antagonists^[31] or vaccines may

be helpful in the future.

On the biological front, mechanisms of virus latent infection/recurrence and analysis of viral gene structure and function need to be further explored using advanced technologies. This might be accelerated by the development of molecular genetics approaches that could draw attention to the genetic conditions of susceptible populations.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

There is no patient involved.

Ethics approval

This article does not contain any studies with human participants or animals.

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