

Herpes simplex virus encephalitis (HSE)

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What is herpes simplex virus encephalitis (HSE)?

HSE is a type of infectious encephalitis which happens when herpes simplex virus (HSV) enters the brain. HSV can be of two types: HSV1 and HSV2. HSV1 is mainly associated with infections of mouth and throat early in life often without symptoms, but lately, it has also been associated with genital herpes. HSV2 is associated with genital herpes predominantly in adolescents and adults as it is transmitted through sexual activity.

Around 90% of adults become infected with HSV1 during their life. The virus attaches to, and enters sensory nerves in the throat and moves to nerve cells called 'ganglia' (e.g. the trigeminal ganglia). Here the virus establishes a latent (hidden) and life-long infection. In some people, from time to time, the virus may reactivate to produce recognisable lesions such as cold sores around the lips and nose.

While the virus is widespread, HSE is rare. How HSV gains access to the brain is not known, there are various hypotheses such as via the blood stream or via nerves but there is no definite evidence to support any of the suggested routes to date.

Whichever way the virus gains access to the brain, in the acute illness, the damage that results from the viral infection and associated inflammation is often severe. Typically, the virus is initially present in a part of the brain called the limbic cortex. It may then spread to the adjacent frontal and temporal lobes of the brain. It is the destruction of tissue in these areas together with brain swelling from the inflammation, which causes many of the symptoms.

Symptoms

HSE usually develops over a period of days but the disease can take a variable course, as with other viral infections. This can be due to numerous factors, such as the immunity of the patient. Typically, it begins with very generalised 'flu-like' symptoms followed by neurological deterioration. The most common symptoms including:

- Headache
- Confusion
- Nausea
- Fever
- Seizures
- Drowsiness

If left untreated, the symptoms tend to progress, become increasingly worse, and can ultimately lead to death.

Diagnosis

The rapid onset and development of HSE presents a dilemma to the clinician. During the early stages, when treatment would be most effective, the symptoms can be very general and so there may be several possible diagnoses.

The key diagnostic procedure is a **lumbar puncture (LP)** (spinal tap) to take some of the fluid bathing the brain and spinal cord (cerebrospinal fluid, abbreviated to CSF) for laboratory analysis. One of the tests called the polymerase chain reaction (PCR) is very sensitive at detecting low levels of viruses' genetic fingerprints. This can detect the virus even when blood tests are normal. In general, the test is useful for up to 10 to 20 days after the onset of neurological disease and then usually becomes negative. At this time, a further procedure for the detection of herpes virus antibody in the CSF can be used. This also provides an accurate diagnosis. This latter test is often used as a follow up test if the initial PCR test(s) is negative.

When a patient is admitted to hospital, because of the 'vague' nature of the symptoms (in some cases) a LP may not be performed immediately. This is unfortunate because the LP is an accurate test, which provides a diagnosis at the time when treatment is most helpful to the patient. False negatives occasionally occur if the PCR is done too early, but a repeat should be done at least four days after symptoms began before considering stopping treatment. **However, a PCR test should always be carried out as soon as possible in all suspected cases of HSE.**

Brain imaging by computerised tomography (CT) scan can be utilised to see changes in the brain. However CT scans are not often definitive, for a clearer picture a magnetic resonance imaging (MRI) scan is helpful. An MRI is thought to provide the best visualisation of the temporal lobe (responsible for cognition and memory), the part of the brain that encephalitis most commonly affects, allowing clinicians to pinpoint any changes more accurately. MRI is abnormal in most patients with HSE but a normal MRI does not rule out the condition. Sometimes an electro-encephalogram (EEG) to monitor the brain's electrical activity assists diagnosis.

These procedures, together with careful and continuous clinical assessment, provide data which may be suggestive of HSE but, also importantly, may exclude other conditions.

Treatment

If treatment with a drug called Aciclovir (which reduces replication of the virus) can be started during the first few days of the illness (48 hours), patient outcome is substantially improved. Before Aciclovir, the risk of death from HSE was 70-80%. After Aciclovir was introduced, the mortality rate has reduced to 10-20%. This being said, **it is of utmost importance that Aciclovir is started immediately**, otherwise, the risk of complications post-infection such as cognitive impairments, epilepsy and other issues increase.

But the outcome of HSE is determined by a multitude of factors and cannot always be easily predicted. The provision of high levels of nursing care and the management of complications such as brain oedema (i.e. swelling) are also key factors influencing outcome.

National UK guidelines recommend a minimum 14-day course of treatment with Aciclovir into the veins in adults. Towards the end of this period, the LP should be repeated and PCR analysis of the CSF performed. If the PCR no longer detects HSV the treatment can be stopped; if HSV is identified, the treatment should continue with repeat lumbar punctures at 7-day intervals until the absence of HSV is confirmed. More information on these guidelines can be found in Management of Suspected Viral Encephalitis in Adults and Children, publication found on our website (www.encephalitis.info) or requested from our office (support@encephalitis.info).

Resistance to Aciclovir

In some patients, the symptoms persist despite the treatment with Aciclovir. Very rarely this may be because a resistance to Aciclovir, meaning the drug is no longer effective at being able to inhibit replication of the virus. This is more common in patients with poor functioning immune systems. In this situation, the HSV remains detectable in the CSF and therefore additional or alternative antiviral medications are given.

Relapses and anti-NMDAR encephalitis post-HSE

HSE tends to occur only once. It is rare to relapse later in life. However, in the cases where there is worsening despite on-going treatment (Aciclovir), it may be due to insufficient doses (often based on the patient's body weight) or other complications of encephalitis may have developed, such as seizures. In the unusual cases in whom there is a recurrence of the infectious encephalitis early after stopping treatment (Aciclovir), it may be because the treatment was not given for a sufficient length of time. In these cases, it is often appropriate to restart treatment promptly. Nevertheless, rarely, in some patients, there may be an early recurrence of the encephalitis after stopping treatment that is due to inflammation, even after the virus is cleared.

Rarely, HSE may be followed by the development of a second encephalitis, even once the virus replication is controlled. This encephalitis is autoimmune and characterised by the presence of antibodies in the patient's blood against a brain protein—for example the NMDA receptor. It can present with different symptoms than the first one such as movement disorders, psychiatric symptoms, confusion and abnormal behaviour. The anti-NMDA receptor encephalitis is treated differently to HSE. For more information on this type of autoimmune encephalitis please see the anti-NMDAR encephalitis and Immunotherapy in autoimmune encephalitis factsheets on our website: www.encephalitis.info/factsheets

HSE in pregnancy

HSE in pregnancy is a situation which can be a concern not only to the mother but also to the unborn baby itself. In pregnancy HSE manifests very much the same way as in the general population with the triad of headache, fever and seizures. However due to the physiological changes that are incurred during pregnancy, the presentation of HSE in pregnant individuals can vary.

In terms of risk to the unborn baby, seizures in the mother can pose a serious risk and therefore seizure control is of utmost important. Ideally the patient should be prescribed on the lowest effective dose of anti-epileptic drugs to prevent seizures. It can be a difficult balance as it's the trade-off between effective treatment and ensuring as little drug as possible can reach the foetus.

Women presenting with their first episode of genital HSV in the third trimester should be commenced on oral or intravenous (IV) Aciclovir, with babies born vaginally started immediately on IV Aciclovir. Delivery by caesarean section is advised but is not usually necessary if the genital HSV began in the first or second trimester. All babies born to mothers with a suspected or proven first episode of active genital HSV should be screened for HSV, even after caesarean section delivery. If HSV is detected, intravenous Aciclovir treatment should be started.

HSE in newborns (neonates) and children

HSE in newborns is defined as having HSE within the first four weeks of birth.

A newborn can get infected with the virus in three ways: as unborn baby (in utero), during delivery, and after delivery (from an infected contact). In the past, HSV2 was thought to be the most common type of newborn HSE, but recently in countries such as UK, Australia and Canada, HSV1 predominates.

Symptoms tend to present between 7-21 days. Though symptoms can be very non-specific, they can include lethargy, fever, and convulsions. HSE in newborns is very severe with high mortality or serious disability rates. In newborns, the frontal lobe tends to be affected the most, affecting motor function.

In children, the most common type of HSV is type 1, and generally affects the frontotemporal lobes of the brain affecting cognition and motor function. Presentation can include fever, altered mental state (encephalopathy), decreased consciousness, seizures or focal neurological deficits. Although it can present discreetly with confusion, altered behaviour and sleepiness.

In both newborns and children, the standard treatment is 21 days Aciclovir rather than the adult 14 day course with repeated LP at 7 day intervals after this to ensure clearance of virus before stopping the Aciclovir.

Prevention of HSE in newborns

- Tell your doctor if you are pregnant and have a history of genital herpes.
- If you are visiting a newborn and have an active cold sore, then avoid direct contact with the newborn. Mothers and other care givers/family with cold sores, should practice strict hand washing, cover up the cold sore, avoid oral contact with a baby, and wear a clean surgical mask, until the cold sores are cleared.

Outcomes and prognosis of HSE

The reduction in HSE mortality has led to a paradoxical situation. There are without doubt more survivors, but many may suffer from permanent neurological and/or psychological deficits, for example amnesia (memory loss). Improvements are still needed to both speed diagnosis and improved treatment. As mentioned before, timing is of the essence. Those patients with poorer outcome are associated with a longer delay in starting treatment following admission to hospital.

The most common complication in HSE post-treatment is memory impairment. This is because the temporal lobe is most commonly affected in HSE. Often patients post-infection present with cognitive deficits and impaired memory, in particular short term memory (type of memory). This can often be very disabling, and the patient may require a lot of additional care.

The message is that our understanding of conditions such as viral encephalitis is continually developing. However, these are complex conditions and whilst it is unlikely that all causes of encephalitis will be preventable (in the near future) the prospect for the rapid and efficient diagnosis for many of these conditions will improve during coming years. The consequence of improved and rapid diagnosis is that early treatment—which is so important—can and will increasingly be introduced.

HSE and the risk of developing Alzheimer's

There is some early research which has reported a possible link between HSV1 and Alzheimer's disease. However, it has not been proven that HSV1 actually contributes to causing Alzheimer's disease in humans.

Most patients with Alzheimer's disease have never had HSE and even if there is a link between HSV, it is likely to be just one element in a complex network of different risk factors.

The most important risk factors for Alzheimer's disease are increasing age and genetic factors (such as having a family history of dementia). The most important modifiable risk factors for cognitive impairment are alcohol excess, smoking, limited exercise, and not keeping an active mind for learning.

Vaccination

The development of a vaccine against herpes simplex is underway but has not currently been completed. The World Health Organisation has recently released a website in collaboration with other international organisations that monitors the vaccine status of various sexually transmitted diseases, including genital herpes. This can be found at <https://stiwatch.org/>

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Thank you!

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