

# Herpetic meningoencephalitis

- **HSV typ I** – *herpes labialis* et *oralis* – encefalitis.
- **HSV typ II** – *herpes genitalis* – serous meningitis in newborns.

## Etiology

- **Herpes DNA viruses** include: *HSV* types I and II, VZV, EBV, CMV;
- capable of long-term latent survival in nervous tissue with the possibility of exacerbation infection;
- transmission throughout the year in all age groups - by contact, by air;

## HSV type I

causes severe hemorrhagic-necrotic encephalitis selectively affecting the frontotemporal area, 30% mortality

## HSV typ II

causes serous meningitis - like other viral meningitis.

## Pathological-anatomical picture

- Necrotizing encephalitis (necrosis most often in the cortex of the frontal lobes);
- brain severely swollen at autopsy, sanguineous meninges;
- intranuclear eosinophilic inclusion bodies;
- biopsy shows antigen herpes simplex by immunofluorescence and positive culture within 48 hours.

## Clinical picture

- Non-specific headaches and fever - progress in a few days to seizures with impaired consciousness, focal symptoms correspond selectively to the lower parts of the frontal and temporal lobes;
- olfactory hallucinations, partial seizures with complex symptomatology, behavioral changes;
- involvement of the dominant hemisphere - **aphasia** - one of the main symptoms;
- cerebral edema can cause death (tentorial herniation);
- survival associated with memory defect.

## Diagnosis

- In the acute phase **brain biopsy**;
- after initiating treatment a non-specific positive CT or MRI finding is sufficient;
- at first, normal CT will show frontotemporal hypodensity (necrosis);
- cerebrospinal fluid - multiplication of lymphocytes, higher protein;
- EEG - generalised slowdown with periodic discharges temporally

## Differential diagnostics and therapy

- Dif. dg.: other encephalitis, brain abscess, tumor; jiné encefalitidy, absces mozku, tumor;
- Unlike other viral CNS infections, we have a causal drug - **aciclovir**.
- aciclovir should always be used **immediately if** a herpes etiology of encephalitis is **suspected**, till proven otherwise

## Links

## Similar articles

- Herpes simplex virus • Herpesviridae
- Viral meningitis

## References

1. BENEŠ, Jiří, et al. *Infekční lékařství*. 1. vydání. Galén, 2009. 651 s. s. 179, 527-528. ISBN 978-80-7262-644-1.
2. ↑ SEIDL, Zdeněk a Jiří OBENBERGER. *Neurologie pro studium i praxi*. 1. vydání. Praha : Grada Publishing, 2004. ISBN 80-247-0623-7.
3. ↑ Skočit nahoru k: a b POVÝŠIL, Ctibor a Ivo ŠTEINER, et al. *Speciální patologie*. 2. vydání. Praha : Galén-Karolinum, 2007. s. 297-299. ISBN 978-80-7262-494-2.

## Source

- ws:Herpetická meningoencefalitida
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Herpetic meningoencephalitis is one of the most serious meningoencephalitis in children and adults. Even with the possibility of causal therapy, the diagnosis is often delayed, the disease has a high mortality and the survivors have a high percentage of permanent neurological consequences.

## Etiopatogenesis

### Etiology

Human *herpesvirus* is a DNA virus that includes two important strains:

- Human herpesvirus 1 (**HHV-1**), known as herpes simplex virus 1 (HSV-1), which causes herpes gingivostomatitis that responds to antiviral therapy but even without treatment, is a self-limited disease. In addition to local infections, HSV-1 and HSV-2 are the cause of severe encephalitis. It is more common in adulthood.
- Human herpesvirus 2 (**HHV-2**), known as herpes simplex virus 2 (HSV-2), causes genital lesions. It is the cause of neonatal encephalitis associated with maternal genital infection.
- **HHV transmission:** saliva, genital secretions, blood and vertically. The gateway is most often the respiratory tract, damaged skin and genital mucosa. The virus can also enter the macroorganism intravenously or transplacentally.
- In HSV-1, in primary infections are most common: *primary gingivostomatitis, pharyngitis, keratoconjunctivitis and encephalitis*.
- When the virus is reactivated in herpes labialis in immunosuppressed patients these things may occur: *herpetic stomatitis* or even *esophagitis* or even *dissemination to generalization of infection*.
- In HSV-2, we encounter *neonatal encephalitis* and *genital herpes*.

However, HSV-1 can cause diseases more typical of HSV-2 and vice versa.

HSV primarily affects the medial temporal cortex as well as the frontal and parietal lobes.

### Pathogenesis of the encephalitis

- It is not sufficiently clarified in humans.
- In animal models, the virus is thought to pass to the CNS through peripheral nerves. Virus-induced apoptosis may then play a role in the molecular pathogenesis of the disease.
- Encephalitis mainly affects the **temporal lobes** (60%), separate extratemporal involvement is observed in about 15% of patients.
- In children, herpetic encephalitis is often a manifestation of herpetic primary infection (approximately 80% of children do not have a history of labial herpes). In neonates, the infection occurs during the passage through the birth canal, with a higher risk of infection when the mother acquired herpes during pregnancy. Mothers with pre-existing and recurrent genital herpes have a significantly lower risk.
- It is known that herpes viruses, during primary infection, incorporate their DNA into the genome of host lymphoid or nerve cells. In the latent phase of infection, viral replication in the ganglia is minimal, but weakening of immunological surveillance, especially of specific cellular immunity, can lead to reactivation of the latent infection, which is usually much less intense than primary infection.

## Clinical picture

Development usually occurs within a few hours to a few days. CNS affliction can be clinically manifested either as a mild disease (**aseptic meningitis**) or more often as a serious disease state - **encephalitis**. Likewise, the beginning can be creeping or peracute.

- **Prodromal symptoms** include fatigue, fever (found in most patients), headache, nausea, vomiting.
- This symptomatology is followed by **acute or subacute development of encephalopathy** (behavioral disorders, lethargy or irritability, confusion, dysphasia, aphasia, photophobia), hemiparesis, cranial nerve deficits (paresis nn. VII., VI., III.), Visual field defects, paraesthesia, central limb paresis, vegetative disorders.
- **Focal neurological findings** and focal convulsions usually appear suddenly at the onset of the disease and persist for up to one week. We find focal convulsions in up to 40% of patients. Meningeal signs may be present, but are not common.
- In *newborns and infants*, we observe highly tuned crying, jaundice, respiratory distress, liver dysfunction.
- In *older children*, we can observe personality changes, behavioral disorders, memory changes, dysosmia, dysgeusia, hallucinations, bizarre ideas. These symptoms may appear early in the course of the disease and persist for about a week. They can often act as the onset of an acute psychiatric illness.
- In some patients, we observe a peracute course with progression of impaired consciousness leading to death without signs of focal neurological symptoms.
- Rare symptoms include the development of subacute encephalitis, which mimics psychiatric illness or benign recurrent meningitis. Rarely, HSV-1 can cause brainstem encephalitis, HSV-2 myelitis.
- In children who survived HSV encephalitis we may encounter severe **antegrade amnesia** (quickly forgotten learned) or severe **retrograde amnesia** (personal knowledge and orientation in time, interval even several years, some has poor memories of faces, many have language difficulties), there are also signs of **frontal damage with behavioural disorders**.

## Diagnostics

When HSV encephalitis is suspected, diagnostic tests should be performed as soon as possible and we should never delay the start of therapy.

### **In the diagnosis of herpetic encephalitis, HSV cerebrospinal fluid PCR and CNS MRI have the highest yield!**

- *Basic laboratory tests* are not helpful in diagnosing herpes infections, but they are essential because they can rule out other causes of the disease.
- Due to the symptomatology, a *CT scan* is often necessary in the introduction to rule out a focal lesion of a different etiology. In the diagnosis of HSV encephalitis, CT is evident after 3rd-4th the day of the disease, when it can detect necrotic changes in the temporal area. This option was used earlier, when earlier diagnosis was impossible, but always meant an ex post diagnosis.
- Today, it is replaced by early diagnostics using PCR and MRI.
- The cornerstone of diagnosis and examination are the **lumbar puncture** and **cerebrospinal fluid** examination. In the introduction we demonstrate a typical serous pattern with:
  - mild elevation of proteinorrhea;
  - normal glycorhachia;
  - moderate pleiocytosis with a predominance of mononuclear cells.
- We can also find the presence of erythrocytes and xanthochromatic appearance. Spectrophotometry eliminates artificial bleeding during the actual puncture.
- It is necessary to send cerebrospinal fluid for PCR detection of **DNA for HSV-1 and HSV-2**. HSV PCR is highly specific, with positivity remaining 5 days after initiation of acyclovir therapy. On the other hand, for the first 1-2 days and after two weeks of illness, the result may be false negative. The yield of cerebrospinal fluid examination is proportional to the amount of cerebrospinal fluid collected ("the more, the better"), we should usually obtain > 10 ml of cerebrospinal fluid. Despite the undeniable importance of PCR, it is necessary to realize that even this method does not have 100% sensitivity and specificity. In addition, the "quality" of the results varies according to the experience of the laboratories. Therefore, the diagnosis should always be made with regard to clinical symptomatology and further examination. False-negative results are rare, so many authors consider a negative HSV PCR result in the initial cerebrospinal fluid sample as sufficient evidence to discontinue acyclovir treatment.
- CSF antibody serology may support evidence of antibody response in the CNS.
- **CT scan and MRI:** *MRI* is more sensitive than CT and is now the imaging method of choice. In MRI we find most changes in the medial area of the temporal lobe and at the base of the frontal lobes, the lesions are often associated with cerebral edema, they are bilateral but rarely symmetrical. **Gyrus deletion** due to edema in the T1 image and high signal in the T2 image are considered to be early signs of the disease in the MRI image. After application of the contrast agent, enhancement may be found in the gyros. In neonatal HSV-2, we find **panencephalitis**.
- Another sensitive test for herpetic encephalitis is **EEG**. Indicates abnormality in 4/5 patients. We observe **focal temporal changes and diffuse retardation of activity**. Periodic high-voltage spikes - waves originating from the time domain and complexes of slow waves at 2-3 s intervals - are very telling for herpetic encephalitis. Normal EEG recording is rare, but does not rule out the presence of encephalitis.
- At some workplaces it is possible to perform tomographic isotope methodology using Tc - 99m = SPECT.
- Brain biopsy is an outdated diagnostic method.

## **Differential diagnostics**

In addition to bacterial etiology (borrelia, leptospira) and encephalitis caused by other herpes viruses, it is necessary to exclude other possible agents such as:

- enteroviruses;
- measles virus;
- parotitis;
- HIV;
- adenoviruses;
- RSV;
- rabies virus;
- arboviruses.

We must rule out post-infectious and disseminated encephalomyelitis, which follows the viral disease - neurons are not directly infected with the virus, perivenous inflammation and demyelination located in the white matter are in the foreground (most common agents: EBV, CMV, HHV-6).

Cerebellitis (ataxia, tremor, vertigo, dysarthria, vomiting, fever) may occur in VZV infection approximately one week after rash.

## **Therapy**

Patients with herpetic encephalitis should be treated and observed in the ICU. Base is:

- Thorough monitoring of vital functions.
- Early detection of convulsion (spasm) activity - seizures are very frequent during herpes encephalitis. We initiate anticonvulsant treatment without a clinical correlate if there is a specific finding on EEG. Commonly used benzodiazepines usually stop the spasm, but due to their short action they do not prevent recurrent seizures. Then a continuous administration of midazolam (eg) or a drug with a longer duration of action

- (barbiturates) is necessary.
- Early detection of an increase in intracranial pressure.

We provide patients with adequate nutrition and hydration according to their abilities (parenteral, nasogastric tube, orally). In case of proven intracranial hypertension, we initiate all necessary measures.

Causal medicine are **antiviral drugs**:

- **acyclovir**, (clearly preferred for higher efficacy and lower toxicity), at a dose of 20 mg/kg for adult i.v. every 8 hours in infusion for 21 days. Its side effects are minimal - renal dysfunction is described at high doses (therefore we do not administer acyclovir bolus).
- vidarabine

We should start acyclovir immediately after the possibility of herpetic encephalitis is suspected, we never wait with treatment for the confirmation of the infection. Afterwards, if HSV infection is not confirmed, acyclovir may be discontinued. Mortality was 60-70% before acyclovir treatment and 30% after it.

- In all neonates at the end of acyclovir treatment, we perform control lumbar puncture and re-examine HSV PCR. Its negativity is a requirement for the end of therapy. Subsequently, we switch to valaciclovir treatment in p.o. form for months to years. **Valaciclovir** (Valtrex) after p.o. administration converts rapidly to acyclovir. It is more expensive, but compared to p.o. acyclovir has better bioavailability.
- Adequate **rehabilitation** is also a part of comprehensive treatment.

## Complications

The most common consequences in surviving patients are:

- motor deficits;
- secondary epilepsy syndrome;
- change in mental state.

The consequences are more frequent in patients with delayed treatment. Patients who started treatment within 5 days of the first symptoms have better results. Interestingly, both HSV-1 and HSV-2 have comparable mortality, but HSV-2 has higher morbidity, ie more frequent neurological consequences (motor deficits, convulsions, microcephaly, sight defects). Subsequent psychiatric changes (hypomania, various degrees of amnesia, Klüver-Bucy syndrome), recurrent aseptic meningitis - Mollaret's meningitis are also reported in connection with herpes encephalitis.

### Mollaret's meningitis

It is a recurrent benign aseptic meningitis. Headaches, meningeal symptoms and fever are typical, and neurological symptoms are only transient. In the cerebrospinal fluid we find mixed pleiocytosis with mononuclear cells, polynuclear cells, endothelial cells (Mollaret cells) and elevated gammaglobulins. PCR can detect HSV-2, uncommonly also EBV or enteroviruses. The therapy is only symptomatic, as the symptomatology disappears spontaneously within a few days. Prophylactic administration of acyclovir or valaciclovir may prevent attacks.

## Links

### Source

- MUDr.HAVRÁNEK, Jiří: Herpetická meningoencefalitida

### Similar articles

- Meningitis