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# Encephalitis with herpes simplex virus

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## EDITORIAL

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## **Encephalitis caused by herpes simplex virus can occur as a result of viral reactivation from the central nervous system, spread from other organs and as an immune reaction.**

Encephalitis is an acute or subacute inflammation of brain tissue. Symptoms include fever, altered behaviour, altered consciousness, confusion, headache, seizures and neurological deficit. Viral infections in the central nervous system are notifiable diseases to the Norwegian Surveillance System for Communicable Diseases (MSIS), along with a number of other microbial infections. These infections usually involve meningitis, not encephalitis.

The MSIS system receives 300–400 notifications of viral infections in the central nervous system each year, of which approximately 49 are cases of encephalitis caused by herpes simplex virus (HSV) type 1 and 2 (1). Although HSV-2 is a relatively common cause of meningitis, HSV-1 causes most cases of herpes simplex encephalitis in adults (2). HSV-2 is a cause of encephalitis in neonates and some immunosuppressed individuals (3, 4).

The prognosis of HSV-1 encephalitis is poor. Mortality is 20–30 % (3), and neurological sequelae are common in survivors. Although the risk of sequelae is high, we have seen considerable improvement in some patients, even several months later, so a good amount of time should be allowed before deciding that further improvement is unrealistic.

*«Around two-thirds of cases of herpes simplex encephalitis are caused by reactivation of latent HSV infection»*

Around two-thirds of cases of herpes simplex encephalitis are caused by reactivation of latent HSV infection, i.e. reactivation from a focus in the central nervous system, or by haematogenous spread from another focus. Around one third of cases are due to primary infection (5), either in the face (and spread via the olfactory or trigeminal nerves) or haematogenous spread. Brain damage is probably due to both the viral infection and an immunological reaction (3), but there is much to suggest that the immunological reaction is the main cause (6). Both immunocompetent and immunosuppressed individuals can be affected.

The list of differential diagnoses is long and includes meningitis, circulatory disorders, brain tumours, metabolic or endocrine disorders, intoxication and mental health disorders, as well as other forms of encephalitis. Taking a thorough case history can help to differentiate viral encephalitis from these other conditions. Immunodeficiency and advanced age can influence symptom presentation. Herpes simplex encephalitis can also occur as a complication of other severe HSV infections, for example eczema herpeticum, as described in a case report now being published in the Journal of the Norwegian Medical Association by Dhondup et al. (7). Patients with herpes simplex encephalitis may thus be found in a number of different hospital departments. Since rapid diagnosis and initiation of treatment are important for the prognosis, the threshold for suspicion and appropriate investigation must be low.

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Diagnosis is usually made by detection of HSV on PCR testing of cerebrospinal fluid and MRI of the brain. If HSV is suspected in a rash, a specimen should be taken from the rash for virus detection.

A failure to recover despite treatment or deterioration despite an initial improvement may be due to recurrence, resistance to aciclovir as a result of mutations in the HSV genome involving the viral thymidine kinase that phosphorylates aciclovir to the active substance, or autoimmune encephalitis, which is a common complication of HSV infection. Autoimmune encephalitis has been reported in around a quarter of patients with herpes simplex encephalitis (8) and is usually caused by formation of N-methyl-D-aspartate receptor (NMDAR) antibodies. This complication has been described by Karlberg et al. in another case report in the Journal of the Norwegian Medical Association (9).

Repeated PCR assays and testing for NMDAR antibodies may often be required. Repeat lumbar puncture may also be necessary to reach the correct diagnosis, since a negative result from the first cerebrospinal fluid sample does not rule out the disorder. Repeat MRI scans are also often required in case of both positive and negative MRI findings. Individuals with recurrent herpes simplex encephalitis should undergo investigation for impaired production or lack of effect of type I interferon (10).

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