Herpes simplex virus encephalitis still has an unacceptably high mortality

Herpes simplex virus (HSV) is a human herpesvirus that causes HSV encephalitis (HSE), which is the commonest fatal sporadic encephalitis in humans.1 About 90% of all HSE cases in adults and children are due to HSV-1, while HSV-2 is associated with HSE in neonates, in which there is a disseminated infection, and in immunocompromised patients, such as those with renal transplants or HIV infection.2 While the exact incidence of HSE is not known, it has been estimated at about one case per million per year.3 This figure is probably an underestimate since about 2000 cases occur annually in the United States.4 The neuropathological picture of HSE is characteristic, consisting of an acute necrotising encephalitis that almost always localises, often asymmetrically, to the orbitofrontal and temporal lobes with involvement of the cingulate and insular cortex; neonatal HSE tends to produce a more diffuse pathology.4 Untreated, HSE has an extremely high mortality rate at about 70% with fewer than 3% of survivors returning to normal function.5 Among common central nervous system (CNS) viral infections, mortality in HSE is disproportionately high, taking into account a recent study that showed that HSV infections are responsible for only 11% of cases compared with 29% for varicella-zoster virus,6 another human herpesvirus that is not associated with such a high mortality.

The neuropathogenesis of HSE has intrigued clinicians and scientists for many years, with two of the key questions relating to, firstly, the very low incidence of the condition in the presence of the widespread carriage of latent HSV in ganglionic tissues in healthy people and, secondly, the propensity of the disease process to localise to the frontotemporal region. About 90% of normal people are seropositive for HSV-1 indicating past exposure to the virus, a finding that is consistent with the presence of latent HSV-1 genomes in the trigminal ganglia of 85–90% of people at unselected necropsy.7 Latent HSV-1 periodically is reactivated, either spontaneously or following various triggering events such as trauma, sunlight, immunosuppression, and x-ray irradiation, to cause blisters in the mouth and lips, also known as cold sores.8,9 The question therefore arises as to whether HSE results from reactivation of latent HSV-1 from the ganglia with subsequent spread to the CNS. However, only about 25% of patients with HSE give a prior history of cold sores, an incidence that is no different from that seen in the normal population.1 This issue was clarified by Whitley et al.,10 who used restrictive enzyme analysis of HSV-1 isolates from oral, labial, and brain sites in patients with HSE to show that the latter can result from reactivation of latent HSV but may also follow a primary herpetic infection or a reinfection by a second herpesvirus.11 There is also evidence for the presence of HSV genomes in the CNS of normal patients, which may in principle act as another source of reactivated virus.12

Regarding the site specificity of HSE, the pathway of viral spread is probably more important than cell-type viral susceptibility. The unique anatomical localisation has been thought to result from entry of the virus via the olfactory pathway with spread along the base of the brain to the temporal lobes,13 a view that is supported by the immunocytochemical evidence of HSV antigens in the olfactory tract and cortex, as well as temporal lobes, hippocampus, amygdaloid nucleus, insula, and cingulate gyrus in patients dying from HSE.14 Another suggestion is that HSE may result from viral spread from the trigeminal ganglia to the temporal and frontal cortex,10 a view that is consistent with this known site of HSV latency. The index of suspicion of HSE should always be high for a patient presenting with the typical features of encephalitis such as fever, headache, confusion, and clouding of consciousness. More specifically, HSE is typically associated with a constellation of frontotemporal features with aphasia or mutism, personality change, and focal or generalised seizures, and in some cases coma.12,15 Meningism, focal motor weakness, and occasionally brainstem encephalitis, which may be recurrent, have also been described.12,14 The diagnosis of HSE is usually established from the combination of the clinical and investigative features. Magnetic resonance imaging (MRI) provides the most sensitive method of detecting early lesions and is the imaging of choice in HSE16; if MRI is available it should be the first diagnostic step after clinical assessment. Cranial MRI may show evidence of focal oedema in the medial region of the temporal and orbital surface of the frontal lobes, insular cortex, and angular gyrus.17 Meningeal and gyral enhancement after gadolinium diethylenetriaminepentaacetic acid (DTPA) administration has also been reported.18 However, the MRI may occasionally be normal in HSE.19 Computed tomography may be normal for the first few days after the onset of symptoms.20 When computed tomography is abnormal it usually shows reduced attenuation in one or both frontal or temporal lobes and sometimes areas of hyperintensity representing small haemorrhages21 and with midline shift in about 50% of cases in one retrospective study.22 Where available, single photon emission computed tomography, while not diagnostic, may provide functional imaging evidence of HSE.23 The EEG is invariably abnormal in HSE.24 While non-specific slowing may be the only feature early in the illness, the later stages are more likely to be associated with high voltage periodic lateralising epileptiform discharges. If present they are diagnostically useful but they are not specific for HSE.25

Examination of the cerebrospinal fluid (CSF) is of considerable diagnostic value in HSE and should always be performed after computed tomography or MRI. The exception, in our view, is where cranial imaging shows evidence of severe cerebral oedema and brain shift, in which case we prefer to delay lumbar puncture until the oedema is reduced with steroids or mannitol because of the risk of brain herniation. While about 5% of patients have normal CSF,10 the characteristic profile consists of a normal or raised pressure, a lymphocytic pleocytosis26 (typically 10–200 cells/mm³), normal glucose, and increased protein (0.6 to 6 g/l). Red blood cells and xanthochromia may be present in the CSF in some patients but are of no diagnostic value in distinguishing HSE from other causes of encephalitis.8 CSF polymerase chain reaction (PCR) for HSV DNA has been a major diagnostic advance and has helped to identify different patterns of HSV infection of the CNS. In an experienced laboratory a PCR test for HSV in the CSF of a patient with HSE during the first week can detect viral DNA in about 95% of cases.27 False negative results are most likely to occur very early, for example, within the first 24–48 hours, or late, for example, after 10–14 days, during the course of the illness.28 The specificity of the PCR test is also excellent, probably over 95% in experienced laboratories with the ability to avoid contamination.29 So that a positive result in the CSF is powerful evidence of HSE. Another great advantage of PCR for HSV detection is that the
of use both diagnostically and in neu-

are extremely high (95% and > 99%,
HSE, as both its sensitivity and specificity
the diagnosis of HSE is suspected.

analogue acyclovir (acycloguanosine) es-

improved by the advent of the nucleoside
patients with HSE have been dramatically

consider doing a brain biopsy in a patient

impossible in HSV infected cells. Its non-toxicity
DNA polymerase and is activated specifi-

clovir selectively inhibits the HSV specific

studies on the CSF of large groups of

point at which treatment decisions have

within 24 hours, as opposed to anti-HSV
assay can be completed quickly, typically

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acyclovir in northwest England.

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cancerous infections and emerging pathogens.

acyclovir has been reported in the
ent patients,

acyclovir resistance in proven HSE has not
been shown to occur in immunocompet-
ent patients, although HSV resistance to
acyclovir has been reported in the
immunocompromised. Whether intra-
venous acyclovir treatment should be fol-
lowed by the use of valacyclovir orally19
for an extended period is an issue that has yet
to be resolved. Despite these remarkable
advances in treatment, HSE still has an
acceptably high mortality (20–30% with
acyclovir18, 19) and morbidity. A better outcome
is seen in younger patients below the age of 30 years and in those in
whom the duration of encephalitis was
four days or less and the Glasgow
score was above 6 when acyclovir was
started. 11 However, patients who have
been treated very early in the illness and
who appear to have made a good recovery
may still be left with significant neu-
ropsychological and neurobehavioural
impairment that may leave them perma-
nently disabled and unable to return to
work. There is still a pressing need to
develop yet more effective treatments for
HSE.

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