



## **Herpes Simplex Encephalitis (HSE)**

*Dr Graham Cleator, Head, Division of Virology, Clinical Sciences Building, Manchester Royal Infirmary*

*Revised by Dr Nick Davies, St Mary's Hospital, London*

Herpes simplex viruses belong to a group of viruses called the human herpes viruses. Other members of the group include:

- Varicella zoster (VZV) - the cause of chickenpox and shingles.
- The Epstein-Barr virus (EBV), the cause of glandular fever.
- Cytomegalovirus (CMV), another virus occasionally causing a glandular-fever-like illness.
- Other more recently described human herpes viruses are human herpes viruses 6,7 and 8 (HHV-6,7, & 8). The role of these viruses in causation of human diseases is not, as yet, fully explained.

Herpes simplex encephalitis (HSE) occurs at any age, to either sex and at any time of year. In the UK up to 200 cases per annum are recorded but, because the condition is probably under diagnosed this figure is presumably an underestimate of the true incidence of the condition.

Infection by HSV-1 (Herpes simplex virus – type-1) usually occurs early in life through asymptomatic infection of the mouth and throat. The virus attaches to and enters sensory nerves in the throat and moves within these nerves to nuclei in collections of nerve cells called “ganglia” (e.g. the trigeminal ganglia) Here the virus establishes a latent, life-long infection. Because most individuals are infected with the virus early in life this means that a high proportion of the population carry herpes simplex virus in latent form, i.e. they are infected for life. In some people this may, from time to time, reactivate to produce recognisable lesions, i.e. cold sores around lips and nose.

While HSV-1 is widespread, HSE is of course rare. How HSV gains access to the brain is not known, but here are various hypotheses. Firstly, viruses may enter the brain from the blood stream. To do this the virus must be small, present in large numbers and able to cross the blood/brain barrier (BBB). Taking into account the properties of the virus this is a possible but probably infrequent route of entry to the central nervous system (CNS). Secondly, there is a direct route, via nerves, from the nose to the olfactory lobes of the brain. This route of infection certainly occurs in various animal “models” of HSE but the relevance to the human disease is uncertain. The virus may “move” from its site of latency via nerves to the base of the skull, cross the meninges and infect the brain. There is however little evidence to support this suggestion. A further possibility is that the virus moves from its site of latency in the trigeminal ganglia “backwards” to the spinal cord and then upwards into the brain. The appropriate nerve pathways exists to support this suggestion but to date there is no definite evidence to support this or indeed any of the other suggested routes.

Whichever way HSV-1 gains access to the brain, in the acute illness, the damage that results from the viral infection and associated inflammation is often severe. Early in infection, the virus shows a distinct predilection for certain parts of the brain. Typically it is initially present in the limbic cortices. It may then spread to the adjacent frontal and temporal lobes. It is the destruction of tissue in these areas together with brain swelling from the inflammation which causes many of the symptoms associated with HSE.

HSE usually develops over a period of days but, like any other viral infection, depending, for example, upon the immunity of the patient, the disease may take a variable course. Typically it begins with “flu-like” symptoms followed by neurological

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deterioration which may include personality and behavioural changes, and perhaps fits and dysphasia. If untreated it may lead to progressive impairment of consciousness, coma and 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, so there may be several possible diagnoses.

Most hospitals do an EEG (an electro-encephalogram to monitor the brain's electrical activity), plus brain imaging by a CT scan (computerised tomography), or, for a clearer picture, an MRI (magnetic resonance imaging). These procedures, together with careful and continuous clinical assessment provide data which may be suggestive of HSE and, importantly, may exclude other conditions. However the diagnostic procedure now accepted as providing an aetiological diagnosis of HSE is the polymerase chain reaction (PCR). This is a test that has been developed using the methods of modern molecular biology. PCR is not used exclusively for the diagnosis of HSE but is also used in many other areas of research and diagnosis. In principle the test is simple (they always are when they have been developed!) but because the test is so sensitive great care must be exercised at all stages of the procedure. The risk of producing false results is always present especially if suitable care and precautions are not taken during taking specimens and in the PCR laboratory.

### Polymerase chain reaction

The principle of the PCR, in this context, is that when the herpes virus infects the brain it will infect cells and multiply. During this multiplication the virus produces more and more new virus particles. Each particle consists of virus DNA and a protein coat. It is the viral DNA which carries the relevant information which leads to new rounds of multiplication etc. Some of this DNA will spread from the site of infection and be liberated into the cerebrospinal fluid (CSF). The CSF is the fluid which is found in the ventricles of the brain and circulates down through the spine and back to the brain. It is the fluid which is taken during a lumbar puncture. When a patient is admitted to hospital with suspected HSE a lumbar puncture should be taken immediately and a sample sent to the virus laboratory for examination by PCR. Other laboratory and diagnostic tests will be carried out at this time and acyclovir therapy started as soon as the CSF has been taken. The CSF may contain only a few copies of the viral DNA. These are undetectable by most laboratory procedures even though they are there! What the PCR does is to produce, in the laboratory, many more copies (millions more) of the original DNA. So much new DNA is produced that it can be easily detected. The new DNA can also be tested to ensure it is really herpes virus DNA and not a contaminant. This data is the important laboratory diagnostic information that the clinician needs. If the sample can be transported to a suitable virus laboratory rapidly a definitive aetiological diagnosis can be produced within a matter of hours. In our laboratory and others throughout the world we have demonstrated that an accurate diagnosis is possible on the first day or two of neurological illness i.e. when the patient may only be showing minimal symptoms. In general, the test is useful for about 10 - 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 (ideally) used as a follow up to the initial PCR test(s).

These developments mean that a specific diagnosis can be reached rapidly. However there are always problems! Firstly not all laboratories are equipped to perform the relevant PCR test. These tests are expensive and specialist laboratory facilities are needed. This means that CSF samples may have to be transported considerable distances, with a consequent time delay, before a test is carried out. Also when a patient is admitted to hospital, because of the 'vague' nature of the symptoms (in some cases) a lumbar puncture may not be performed immediately. This is unfortunate because we now have an accurate test which provides a diagnosis at the very time when treatment is most helpful to the patient. The situation is further confused because the attending clinician may be faced with a very difficult situation if the symptoms are vague and perhaps suggest a diagnosis other than encephalitis. However, a PCR test should always be carried out as soon as possible in all suspected cases of HSE. It is now clear that the clinician needs as much information as possible on how the virus laboratory can be used in helping to resolve diagnostic problems.

Lastly, concerning diagnosis, it is important to understand that even with the use of PCR diagnostic problems still remain. False PCR results can occur. In the future procedures may be introduced to minimise this problem. It is clear that, although PCR plays a central role in the diagnosis of HSE, other procedures for patient evaluation including clinical examination, brain imaging etc. are of crucial importance in helping to recognise the disease at the time when the patient is admitted to hospital. The combination of clinical skill and the interpretation of all the investigative data as well as PCR results are all important. The correct pathway to rapid and efficient diagnosis clearly necessitates high levels of clinical skills together with the informed use of laboratory procedures, in particular PCR. Diagnosis of HSE therefore requires close collaboration between clinical and laboratory staff.

## TREATMENT

The role of Acyclovir is central to the treatment of HSE. If therapy can be started during the first few days of the illness there is a dramatic reduction in the mortality rate - c.80% down to 25%. The provision of high levels of nursing care and the management of complications such as brain oedema (i.e. swelling) are also key factors which may influence the outcome of HSE. As experience with the use of Acyclovir has grown it has become apparent that the currently accepted 10 day course of treatment may not always be sufficient to provide effective treatment. Rare cases of "relapse" of encephalitic illnesses have and are being noted. Trials of new treatment protocols are currently under consideration and no doubt will be implemented in an effort to provide more effective treatment. Also new derivatives of Acyclovir have been produced and have the potential to improve the outcome of HSE still further. Some of these new drugs have been purposely "designed" to have properties which will allow them to gain access to the brain more efficiently than Acyclovir. If these drugs are introduced for the treatment of HSE the prospect for the clinical outcome of patients improves still further.

The reduction in 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). For a child with a potentially long life ahead this is a particularly distressing situation. Improvements are still needed in both diagnosis and treatment.

Recent recognition of mild cases of HSE and the suggestion that latent infection of the brain can occur add a further dimension to this disease. If a patient suffers repeated episodes of mild (undiagnosed and not debilitating) HSE, there could be progressive damage to the brain. The relationship of such episodes to the development of various psychological disorders must now be given serious consideration and form the basis of future research programmes.

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 encephalitis will be preventable (in the foreseeable 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.

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The Encephalitis Resource Centre, 7B Saville Street, Malton, North Yorkshire YO17 7LL UK  
Information: +44 (0) 1653 699 599 Administration: +44 (0) 1653 692 583 Fax: +44 (0) 1653 604 369  
Email: mail@encephalitis.info Website: www.encephalitis.info

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