Imaging and laboratory investigation in herpes simplex encephalitis

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Abstract
A 14 day old baby presented with signs of an acute encephalitis. Clinically, herpes simplex encephalitis (HSE) was suspected. Early MRI and EEG were normal and there was rapid clinical improvement. A negative polymerase chain reaction (PCR) result on the initial CSF sample seemed to make HSE most unlikely. This diagnosis was subsequently proved after demonstration of specific antibody production using immunoelectrophoresis of the CSF. The child had extensive damage to brain tissue. The need for sequential analysis of CSF in making or refuting this diagnosis is illustrated.

Keywords: herpes simplex encephalitis; diagnosis; imaging

Of all the causes of acute encephalitis, herpes simplex virus is associated with a particularly poor prognosis. Neonatal herpes simplex virus infection has been reported to occur in up to 0.03% of new-born infants. Untreated, herpes simplex encephalitis, even without dissemination, carries a mortality of around 50% and a very high incidence of subsequent neurological abnormality in survivors. It is essential if at all possible to establish a precise microbiological diagnosis to plan therapy and guide prognosis. The polymerase chain reaction (PCR) is reported as a rapid and reliable test for the diagnosis of herpes simplex encephalitis, but definite laboratory diagnosis of the cause of infective encephalitis can be very difficult in practice. Examination of CSF for production of specific antibody to HSV is a parallel approach to the search for viral DNA by PCR.

Case report
A male infant aged 14 days presented with an 18 hour history of poor feeding, vomiting, and jerking movements. He had been born at full term by normal delivery after an uncomplicated pregnancy. Routine examination at neonatal discharge was normal. On admission he had a low grade fever, was irritable, and had decreased truncal tone. His fontanelle was normotensive. He was started immediately on broad spectrum antibiotics and acyclovir with an initial diagnosis of infective encephalitis. Blood count and biochemical screen including glucose, calcium, and magnesium were normal. The white cell count in CSF was mildly raised at 40 cells/mm³, red cell count was <5 cells, and protein concentration was normal. Bacterial and viral culture of CSF was negative as was herpes simplex PCR. There was insufficient sample to test for intrathecal antibody. He showed considerable clinical improvement within 24 hours but remained somewhat hypotonic for 48 hours. Occasional jerky movements (not frank fits) continued for 3 days.

Cranial ultrasound on admission was thought to be normal as was brain MRI (without contrast) at 48 hours (figure A). An EEG performed on the same day as the MRI showed normal background activity and no seizures. Intravenous antibiotics were discontinued once CSF bacterial culture was known to be negative. Acyclovir was discontinued at 7 days when the PCR result became available. He was asymptomatic and feeding well.

At review 1 week later he was asymptomatic and thriving. Examination 2 weeks after presentation was normal but the cranial ultrasound was abnormal with increased frontal and parietal echogenicity. Brain MRI at this time showed widespread abnormalities with areas of haemorrhage and tissue loss in the frontal and parietal regions (figure B). In the absence of evidence of bacterial infection or severe hypoxic ischaemic insult, the most likely pathology in this age group to account for such rapid and extensive change in MRI appearance is herpes simplex encephalitis. He was readmitted for intravenous acyclovir. The EEG was repeated and was again normal. Repeat serum and CSF showed raised total protein in the CSF (1.3 g/l), raised CSF IgG (0.13 g/l), and oligoclonal bands on electrophoresis indicating the production of intrathecal antibody. A band indicating specific antibody to HSV was found on immunoelectrophoresis of the patient’s CSF against herpes simplex virus antigens. This clearly established herpes simplex virus as the cause of the illness.

The source of the baby’s infection remains unknown. His mother had no evidence of herpes simplex virus infection and the antigen gel used for electrophoresis does not distinguish type 1 from type 2. After the second admission to hospital, both the initial CSF sample before
any treatment and the second were retested by PCR at two reference laboratories using all available techniques. They were both negative. The child remained well throughout the second admission and was discharged on oral acyclovir, which was continued for 6 months. A third CSF sample 2 months after the initial presentation was also examined by immunoelectrophoresis against herpes simplex virus antigens and showed denser and sharper oligoclonal bands indicating increased production of herpes simplex virus antibody with greater specificity; a PCR was again negative. At this time, the MRI showed significant further deterioration with extensive white matter and cortical breakdown at the sites of damage seen on the second scan (figure C).

By 6 months of age he exhibited some mild dystonic posturing of the left arm. At 15 months he could sit and roll but not crawl and had signs of a left sided hemiplegia. His general development was 4–5 months delayed and he has had seizures requiring treatment with carbamazepine.

Discussion
The clinical suspicion in the first instance was herpes simplex encephalitis but this was rejected in the light of normal imaging (ultrasound and MRI), normal EEG, and negative PCR on CSF. Acyclovir was discontinued after only 7 days. A week later the child was found to have marked destruction of brain tissue. The diagnosis of herpes simplex encephalitis was confirmed by immunoelectrophoresis of CSF whereby specific binding of antibody to a gel impregnated with herpes simplex virus antigens is visualised by staining for human IgG.5 This was underscored by maturation of the specific antibody response over time. Had the initial PCR result been positive, 21 days of intravenous acyclovir would have been given. We cannot be certain whether this would have improved the outcome but this remains a distinct possibility.

Early ultrasound in cases of herpes simplex encephalitis may show areas of increased echogenicity but is often normal.6 Early white matter oedema is not easily distinguished from unmyelinated white matter, which may account for the early MRI being reported as normal.7 Our review of the initial MRI suggests that it may in fact not have been quite normal (figure A). Gadolinium might have increased the sensitivity of the scan but was not employed in this case.

Herpes simplex virus causes severe structural damage to the neonatal brain with haemorrhagic necrosis leading to formation of cysts as the series of MRI images from this case clearly illustrates. A PCR on CSF in herpes simplex encephalitis has been reported to be...
very sensitive for the diagnosis,\textsuperscript{3,4} but as we have shown, great care must be taken in interpreting a negative result if there is strong clinical suspicion. We have no adequate explanation as to why the PCR was negative on three occasions including the sample before any treatment in this definite case.

The consensus report on diagnosis of herpes simplex encephalitis which was published in 1996 recommends that therapy with acyclovir should be instituted without delay once the diagnosis is suspected and that CSF examination both for viral nucleotide sequences by PCR and for evidence of intrathecal antibody should be employed.\textsuperscript{9} Normal ultrasound, MRI, and EEG early on and lack of specific clinical signs cannot be taken as evidence for the absence of disease. This case underscores the consensus recommendation for cases of suspected herpes simplex encephalitis that even if the initial CSF sample is negative both for antibody and viral genome, a second sample after an interval should be similarly analysed before cessation of acyclovir is contemplated.\textsuperscript{9}

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*J Neurol Neurosurg Psychiatry* 1999 67: 243-245
doi: 10.1136/jnnp.67.2.243

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