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15 min consultation: Managing neonatal and childhood herpes encephalitis

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ABSTRACT

Herpes simplex encephalitis (HSE) is the most common single cause of viral encephalitis in infants and children. Treated or untreated, it can be associated with considerable morbidity and mortality, and its presentation is usually investigation is important in order to establish the diagnosis so that treatment can be optimised. We address some common questions arising when diagnosing and treating presumed HSE throughout childhood.

Composite case vignette: a 9-month-old girl with herpes simplex encephalitis

A previously well 9-month-old girl presented with fever and a 40 min focal seizure. She was started on intravenous ceftriaxone and aciclovir, intubated and ventilated. An MRI brain scan on day 1 demonstrated features consistent with focal encephalitis with left frontotemporal lobe involvement. After stabilisation, lumbar puncture was performed. One week later, the PCR result confirmed herpes simplex type 1 infection. She completed 3 weeks of intravenous aciclovir via a peripherally inserted central catheter line at a dose of 500 mg/m^2 three times daily. Repeat MRI brain scanning on day 14 showed extensive destruction of the left hemisphere.

After completion of the treatment course, she was commenced on 3 months of oral antiviral prophylaxis. Two months after completing this, she suddenly became encephalitic with behavioural change and choreoathetoid movements. She had facial dyskinesia and numerous non-purposeful movements, but no fever. Intravenous aciclovir was restarted at 500 mg/m^2 TDS, and this was continued for 21 days although no herpes simplex virus (HSV) was subsequently detected by PCR in the cerebrospinal fluid (CSF). Further investigations revealed that the patient had developed autoantibodies to a neurotransmitter receptor. She remains severely disabled, requires feeding via gastrostomy tube and requires 24 h care.

Composite case vignette 2: neonatal herpes simplex encephalitis

A term baby presented on day 15 of life with poor feeding, fever and lethargy. His transaminases were raised and there was disseminated intravascular coagulation. High-dose intravenous cefotaxime and intravenous aciclovir (20 mg/m^2 TDS) were initiated immediately. Despite fresh frozen plasma and vitamin K, a lumbar puncture (LP) was deemed unsafe for several days. HSV type 2 was detected on blood PCR. A brain MRI scan on day 2 was normal. On day 21 of intravenous aciclovir, the baby had a 'proof of cure' LP and a repeat MRI. The latter was now abnormal, with several punctate haemorrhagic foci within the deep cerebral white matter. The CSF PCR was positive for HSV-2. Intravenous aciclovir was finally ceased after a negative HSV PCR result at week 6. The baby was prescribed oral aciclovir prophylaxis until the age of 15 months. Three months after discontinuing prophylaxis, he had a further episode of herpes encephalitis. Oral antiviral prophylaxis was recommenced for a further 3 years. At age 5 years, he is neurocognitively normal and doing well at primary school.

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WHAT ARE THE PRESENTING FEATURES OF NEONATAL AND CHILDHOOD HERPES SIMPLEX ENCEPHALITIS?

Herpes simplex encephalitis (HSE) is a devastating disease that can be difficult to diagnose in its early stages. By definition, neonatal herpes simplex (HSV) disease presents in the first 4 weeks of life and is almost always acquired by perinatal exposure to HSV. Illness symptoms often begin between the first 7–21 days of life. There is a spectrum of clinical syndromes; encephalitis is the most serious presentation, usually associated with lethargy, fever and convulsions. Identifying the source of HSE in neonatal disease can be difficult as a history of known maternal HSV disease (genital or occasionally oral) is not universal and maternal disease may be asymptomatic.

Childhood HSE presents with similar features: fever, altered mental state (encephalopathy), a deteriorating level of consciousness, focal seizures or focal neurological abnormalities. The infective source is usually elusive. Parents can describe encephalopathy as a change in behaviour, sleepiness or confusion. Children with normal behaviour at presentation may become confused later as the encephalitis progresses.

DOES A CHILD WITH HSE HAVE TO HAVE EXTERNAL LESIONS FOR THE DIAGNOSIS TO BE LIKELY?

In neonates, skin lesions may be present. However, they may appear later in the clinical course than the presenting fever, lethargy or even seizures. In childhood HSE, only 10% have a prior history of mucosal symptoms such as cold sores or conjunctivitis.[1] Therefore, diagnosis requires a high index of suspicion.

HOW COMMON IS HSE?

Neonatal disease is more common than childhood disease. The incidence of severe disease in infants is 1 in 64 000 infants per year. In children over 1 year, HSE is nearly four times less common, occurring in 1 in 230 000 children per year.[2]

HOW DO I MANAGE HSE?

Start antivirals urgently when HSE is suspected—earlier treatment is associated with a better outcome. Assess the child carefully for seizure activity, which may be subtle, and treat this promptly in order to avoid further increases in intracranial pressure. Involve the intensive care team early as infants and children with HSE can deteriorate quickly. Ensure adequate hydration as high-dose aciclovir can cause acute renal failure.

SHOULD A LUMBAR PUNCTURE ALWAYS BE ATTEMPTED IN HSE?

CSF testing is an essential component of the diagnostic work-up; see box 1 for CSF investigations in children with suspected encephalitis. CSF should be tested as soon as it is safe to perform an LP in any child with suspected encephalitis. CSF can show lymphocytes or neutrophils.

It is common that insufficient CSF is obtained and it is important to take enough for local laboratory requirements. Children produce approximately 0.35 mL/kg of CSF per hour, and it is safe to take up to 0.2 mL/kg CSF, typically 1.5–2 mL (60 drops) from a 10 kg child and more from older children.[3]

Box 1 Cerebrospinal fluid investigations for the initial investigation of encephalitis[4]

- If possible, measure the opening pressure with manometry. A raised pressure indicates that a meningo/encephalitic process is likely.
- Microscopy, culture and sensitivity analysis for bacteria.
- A broad first-line virus screen in encephalitis would include PCR for herpes simplex virus (HSV)-1 and HSV-2, VZV, enterovirus, parechovirus, EBV, HHV6, mumps. The differential is wider in children with impaired immunity.
- A biochemistry sample for glucose (with paired blood), lactate and protein.
- Additional sample should be saved for further testing–such as antibodies or oligoclonal bands (with paired serum sample).

DOES IT MAKE A DIFFERENCE IF THE PCR IS POSITIVE FOR HSV-1 OR FOR HSV-2?

No, not really. HSV-1 is more common in childhood HSE. HSV-2 tends to be associated with genital herpes and is more common in neonatal HSE. Although neonatal disease is often more severe than childhood HSE, the HSV type does not dictate this and devastating HSE disease can occur in both age ranges.

WHAT IS THE BEST NEUROIMAGING MODALITY?

Children presenting with an altered mental state and a fever may have a CT scan, preferably with contrast, to look for space-occupying lesions—tumours, abscesses or haematomas. However, MRI is better than CT for the diagnosis of encephalitis, so at least one brain MRI scan should be performed during the acute clinical course. A normal MRI does not rule out HSE, particularly early in the course of the disease, so it should be repeated after 4–7 days if suspicion remains. This information will contribute to diagnostic certainty and aid decision making about stopping or continuing the acute antiviral treatment course.

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IS AN EEG REQUIRED?

Even after LP and MRI, there can be diagnostic uncertainty about HSE, and an EEG may provide additional diagnostic clues. The typical pattern is of periodic lateralising epileptiform discharges in the temporal lobe, with slow wave complexes occurring at intervals of 2–3 s. While these are strongly associated with HSE, they can be seen in other disorders including space-occupying lesions, so the triad of investigations —CSF analysis, MRI and EEG—are the diagnostic gold standard.

WHAT THERAPY IS RECOMMENDED WHILE WAITING FOR THE INVESTIGATION RESULTS?

There is considerable clinical overlap between patients with encephalitis, meningitis and septic shock. Therefore, patients are usually prescribed broad-spectrum antibiotics and high-dose aciclovir until test results are available. Because of the severity and the non-specific presentation of neonatal disease, some clinicians start aciclovir in all neonates less than 21 days of age in whom antibiotic therapy is being given empirically for suspected sepsis,[5] although others have cautioned that aciclovir is inappropriately or excessively used in children of all ages.[6]

WHAT IS ADEQUATE TREATMENT?

High-dose intravenous aciclovir is most effective when started early. Following disease relapses in early aciclovir studies in neonates, the standard of care became high-dose intravenous aciclovir given for 21 days for neonatal HSE.[7] However, there are no published randomised controlled trials (RCTs) on dosing or duration for HSE treatment of older children. Table 1 gives an overview of HSE treatment. Maintaining intravenous access for the required duration of the aciclovir course can be problematic, so early insertion of a PICC line once the diagnosis is strongly suspected or confirmed can be very helpful. Repeating an LP at the end of 21 days of treatment to ensure a negative CSF PCR result is associated with a better outcome,[8] but this is not universal practice. Centres that advocate a 'proof of cure' LP recommend continuing intravenous antiviral therapy where the day 21 CSF remains HSV PCR positive, especially in neonatal disease.[8] There is no place for oral aciclovir or valaciclovir in the treatment of acute HSE given the potential disease severity. Nor is there any evidence to support steroid use in childhood HSE.

IS ACICLOVIR RESISTANCE AN ISSUE?

In immunocompetent patients, viral resistance to aciclovir occurs rarely and is not clinically significant, the reported prevalence being less than 1%.[12] However, in immunocompromised patients, this figure rises to 6%. The degree of immunosuppression, duration and frequency of exposure to aciclovir appear to be the most important risk factors for resistance. Resistance testing should be requested from a reference laboratory when suspected. Second-line drugs include foscarnet or cidofovir.

IF HSE IS UNLIKELY, WHEN IS IT SAFE TO STOP ACICLOVIR?

This is a notoriously difficult decision. If doubt exists, a full course of aciclovir should be given risking overtreatment rather than undertreatment. Where clinical suspicion of HSE is low, it is usually appropriate to stop aciclovir if

- there is a negative CSF HSV PCR and cell count (<5 cells/mm^3) and
- normal MRI neuroimaging and
- normal EEG and
- a full and rapid clinical recovery with normal level of consciousness or
- an alternative diagnosis becomes apparent.

DOES A NEGATIVE LP RULE-OUT HSE?

Aciclovir should not be stopped if the CSF is negative on PCR for HSV when other features are consistent with HSE, particularly CSF cell count, MRI findings or EEG. Note that HSV PCR is a highly sensitive and specific test (94 and 96%, respectively), except during the first 24 h of the disease, when as many as 10% of HSE CSF samples can be falsely negative.[13] If suspicion of HSE remains after an initial negative CSF PCR, a second LP and HSV PCR should be performed before day 4 of treatment.[6] In addition, if aciclovir treatment is started some days before CSF is obtained for analysis, the PCR result may be falsely negative; HSV PCR results are unlikely to be affected by <48 h of aciclovir therapy and may still be informative up to a week after therapy is started.[14]

CAN NEONATAL AND CHILDHOOD HSE RECUR?

Since the introduction of high-dose, prolonged therapy for neonates and children with proven or suspected HSE, early relapses are less common. Children presenting with features suggestive of HSV relapse need repeat cultures of blood and CSF, including CSF PCR for HSV and autoantibody quantification (see box 1).

After neonatal HSE, HSV can reactivate months to years after the initial infection, mostly presenting as dermal flares, or as an encephalitis as devastating as the initial illness.[15] It is thought that early-life infection impairs the development of an effective adaptive immune response,[1] but prolonged antiviral prophylaxis can prevent recurrence (see below).

Outside the neonatal period, HSE can signify the presence of underlying immunodeficiencies in the innate immune system associated with defective virus recognition, particularly in the TLR3 pathway.[16] These children can develop protective adaptive immune responses. Though there are little data, older

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Table 1 Treatment of herpes simplex encephalitis (HSE)* (assuming normal renal function and hydration)[7 9 10]

Birth to 3 months	All children >3 months
Intravenous aciclovir 20 mg/kg TDS for at least 21 days	*Intravenous aciclovir* 3 months to 12 years: 500 mg/m^2 TDS for 21 days Over 12 years: 10 mg/kg TDS for 21 days

Prophylaxis against HSE recurrence

Birth to 3 months	Immunocompetent children >3 months	Immunocompromised children >3 months
Aciclovir per os (PO) 300 mg/m^2 TDS for at least 12 months[7] *Oral vacaciclovir*: Not recommended—no neonatal data	*Aciclovir PO* 300 mg/m^2 TDS for at least 3 months *OR* 1340 mg/m^2 BD for at least 3 months[11] *Valaciclovir PO*: 1 month to 12 years 25–40 mg/kg TDS for at least 3 months	*Aciclovir PO* 300 mg/m^2 TDS for at least 12 months *OR* 1340 mg/m^2 BD for at least 12 months[11] *Valaciclovir PO*: 1 month to 12 years 25–40 mg/kg TDS for at least 12 months

*Dosing information: oral aciclovir is available as suspension at either 400 mg/5 mL (preferred) or 200 mg/5 mL. It is also possible to use reconstituted dispersible tablets (200 and 400 mg available). For valaciclovir, there is no approved liquid preparation. A palatable, red suspension can be prepared by pharmacists from crushed tablets (shelf life under refrigeration=28 days).
BD, twice daily; TDS, three times daily.

children are not routinely given antiviral prophylaxis beyond the first 3 months.

Both neonatal and childhood HSE predispose to subsequent autoimmune encephalitis, with new neurological symptoms, including aphasia, behavioural change, choreoathetoid movements and opercular syndrome.[15] This may require immunomodulatory treatment with neurology advice.

WHAT ABOUT PROPHYLAXIS AFTER HSE?

Prophylaxis with aciclovir has been shown to reduce HSV relapse.[15] While 12 months of antiviral prophylaxis is adequate for some children following neonatal HSE, late central or dermal flares may indicate that longer-term or even lifelong prophylaxis may be required. Findings from a small patient series proposed doses of 1340 mg/m^2 aciclovir given twice daily (total daily dose 2680 mg/m^2),[11] based on CSF penetration data, but a more recent larger placebo-controlled RCT validated oral aciclovir given at 300 mg/m^2 three times daily (900 mg/m^2) as adequate at improving neurodevelopmental outcome.[7]

Valaciclovir is the prodrug of aciclovir and has better enteral absorption compared with aciclovir, producing higher plasma and, most importantly, CSF concentrations[9] and permits a more manageable dosing regimen. Oral aciclovir is recommended for neonates and valaciclovir for older children requiring long-term prophylaxis (table 1).

WHAT ADVICE SHOULD WE GIVE TO PREGNANT WOMEN WHO HAVE GENITAL HSV IN THE FINAL WEEKS OF PREGNANCY?

HSV primary infection in the third trimester presents a significant neonatal risk, and delivery by caesarean section is advised followed by neonatal screening for HSV (see below). Babies born vaginally should be started on intravenous aciclovir at birth.[17] Women with primary HSV infection in the first or second trimester should be prescribed oral or intravenous aciclovir, followed by daily suppression with oral aciclovir from 36 weeks of gestation to reduce the chances of lesions being present at delivery.

In recurrent HSV infection, the risks are less, but if active lesions are present at delivery then delivery by caesarean section may be considered. For vaginally delivered babies, there are little data to guide initiation of aciclovir, and there is variable practice. We would recommend minimising the risk of a devastating illness by treating all infants born to mothers with active lesions.[17]

All babies born to mothers with suspected or proven active HSV should be screened for HSV by mucosal (conjunctiva, pharynx, rectum) and skin swabs taken between 12 and 24 h of age, even after caesarean section delivery. If HSV is detected, intravenous aciclovir treatment should be continued/initiated.

WHAT ONWARD REFERRAL IS NEEDED?

Where there is a family history of invasive HSV disease and/or consanguinity, children should be referred to an immunology centre. Identification of defects permits family testing, and consideration of antiviral prophylaxis in HSV-seronegative family members. Even where this is not the case, childhood HSE should be discussed with a local tertiary paediatric infectious diseases specialist with access to specialist paediatric neurologists.

Children with HSE will require long-term multidisciplinary neurodevelopmental follow-up and possibly also psychological and educational rehabilitation following what is often a long hospital stay and

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convalescence. They also may require treatment for longer-term complications, including epilepsy, spasticity and dystonia. Useful contacts for parents and children include charities that offer support to those who have suffered an acute brain injury, such as the Encephalitis Society (http://www.encephalitis.info), Headway and the Child Brain Injury Trust (http://www.headway.org.uk).

CONCLUSION

HSE is a highly destructive neurotrophic virus; early diagnosis with early and optimal treatment offers the best chance to ameliorate the otherwise poor outcome. In neonates, the outcomes can be particularly severe so in any febrile neonate presenting with possible sepsis, neonatal HSE should be considered; where there are other clues to the diagnosis such as deranged liver function tests or skin lesions, babies should be commenced on aciclovir unless an alternative diagnosis is apparent.

All children, irrespective of age, should have CSF sampling when clinically well enough to tolerate this; this is usually on admission but should certainly be early in the disease once stabilised and any coagulation dyscrasias corrected. A repeat diagnostic LP should be undertaken if there is any doubt about the original result. Some infection specialists advocate an end of treatment LP to ensure viral clearance and to guide the need for long-term prophylaxis.

Once high-dose intravenous aciclovir is started, the diagnostic work-up must be completed in order to direct the decision of when to stop antiviral therapy. This includes evaluation of the clinical, microbiological, radiological and neurophysiological findings. If significant doubt persists, continuing intravenous aciclovir for the full 21 days is the only effective way to minimise risk of undertreatment. However, meticulous history-taking and complete and timely diagnostic work-up will minimise unnecessary treatment.

Risk of HSE recurrence differs greatly between neonatal and childhood onset HSE. In neonates, there is now good evidence that long-term prophylaxis improves prognosis and reduces the rate of HSE recurrence as well as dermal flares. In older children, evidence is emerging that HSE may be due to an isolated immunodeficiency so as functional and genetic diagnostics continue to expand all children with possible underlying immunodeficiency need evaluation by paediatric infectious disease specialists following HSE.[18]

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