Introduction

Encephalitis should be suspected in any child with fever, seizures and decrease in consciousness or irritability.

Although this constellation of symptoms is a fairly common presentation in paediatrics, the most serious cause is HSV encephalitis, which untreated has a mortality rate of 70%. Treated, this is reduced to 20%, hence the high index of suspicion and low threshold to treat for this condition.

Other symptoms may include headaches, confusion, altered behaviour, vomiting and focal neurological deficits. There may be a history of fever and general malaise, or the onset may be quite sudden. It can be difficult to differentiate between encephalitis and other causes for the above symptoms, therefore all cases must be considered suspected infectious and treated as such with antibiotics and aciclovir until proven otherwise.

The cause of encephalitis is only found in approximately one third of cases. This is a guideline to investigating encephalitis, which should be used in context with the clinical picture.

History

Including:
- Recent respiratory illnesses or chicken pox
- Travel including swimming in thermal pools
- Family illness or cold sores
- Previous neurological or psychiatric presentations
- Baseline developmental and behavioural status.

Examination

Thorough systems exam.
Full neurological exam including eye and fundal exam, mental state.
Don’t forget careful skin exam for rash, lesions, neurocutaneous markers.
Differential diagnosis

- Bacterial meningitis
- Viral meningo-encephalitis
- Tuberculous meningitis
- Parasitic
- Immune mediated encephalitis
- Demyelinating disorder
- Paraneoplastic disorder
- Epileptic encephalopathy
- Metabolic encephalopathy
- Vasculitis
- Poisoning
- Psychiatric disorder

Initial investigations for all cases

- FBC
- U&Es
- LFTs
- Gas
- Glucose
- NH3 – purple tube on ice
- Cultures
- Take 2 large red tubes (10mls blood) and request storage for serology if needed later
- Lumbar puncture – (if safe to do so –see below)
  Take 4 tubes – MCS, protein, glucose, HSV and VZV PCRs.
  May show pleocytosis, raised protein or raised RBC count or may be normal.
- EEG – looking for generalised slowing and any epileptiform activity
- Neuroimaging - ideally MRI but CT if needed urgently to look for raised intracranial pressure.

Further Investigations

To investigate the underlying cause if not yet found – consider in clinical context

This is not a routine battery of tests but is a guide in the case of a diagnosis not being reached from initial screening. Suggest discussion with the discussed with the Infectious Diseases team or Virology lab (Dr Kitty Croxson).

It is to be used in the immunocompetent child.

Immunosuppressed children should all be discussed with the Infectious Diseases team.
# ENCEPHALITIS – INVESTIGATION & MANAGEMENT

## Laboratory Investigations

<table>
<thead>
<tr>
<th>Blood / Serology</th>
<th>CSF</th>
<th>Urine</th>
<th>Other</th>
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<tbody>
<tr>
<td><strong>Infective</strong></td>
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<tr>
<td>HSV1 + 2</td>
<td>M,C &amp; S Protein Glucose PCRs for VZV, HSV, enterovirus</td>
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<td>NPA if respiratory symptoms CXR Skin swabs Throat / rectal swabs for enterovirus</td>
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<td>VZV</td>
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<td>Enterovirus</td>
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<td>Influenza</td>
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<td>Parvovirus</td>
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<td>Measles</td>
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<td>Mumps</td>
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<td>Rubella</td>
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<td>Bartonella</td>
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<td>Mycoplasma</td>
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<td>Enterovirus</td>
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<td>HHV6</td>
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<td>EBV</td>
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<td>CMV</td>
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<tr>
<td>Consider: TB, HIV, syphilis, amoeba, (Borrelia if been overseas)</td>
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<td><strong>Suggest discussion with either ID team or Dr Kitty Croxen prior to requesting second line virology.</strong></td>
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<td><strong>Metabolic</strong></td>
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<tr>
<td>Glucose</td>
<td>Glucose Lactate Amino acids Pyruvate</td>
<td>Organic acids</td>
<td>Amino acids</td>
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<td>Lactate</td>
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<td>Ammonia</td>
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<td>TFTs</td>
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<td>Copper/ceruloplasmin</td>
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<td><strong>Immune-mediated / Inflammatory</strong></td>
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<td>Oligoclonal bands</td>
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<td>ESR</td>
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<td>ANA, rheumatoid factor</td>
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<td>Auto antibodies (limbic encephalitis panel, Anti GAD, VGKC, Anti NMDAR antibodies) - discuss with neurology</td>
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<td><strong>Others</strong></td>
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<td>Tumour markers</td>
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<td>Toxicology screen</td>
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<td>Lead</td>
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See Appendix 3 for help with lab investigations

**Other investigations**
MRI/MRA – consider MRI spectroscopy if possible metabolic disorder
Management

Initial treatment
Start aciclovir and broad spectrum antibiotics intravenously for any child where there is a suspicion of encephalitis.

Where possible perform the above initial investigations including lumbar puncture (LP) prior to starting treatment. See below for contraindications to LP. If LP is not possible at the time it should be performed as soon as safely possible to allow informed decisions to be made about the duration of treatment.

In the child over 6 months, the most common cause is Herpes simplex. However the PCR may be negative on the first lumbar puncture.

A normal LP does not exclude encephalitis. If there is clinical suspicion aciclovir should be continued until further investigations including a second LP have been performed. Antibiotics should be continued until cultures are negative.

The child should be kept adequately hydrated but with judicious use of fluids, bearing in mind the risk of SIADH and cerebral edema.

Baseline renal function should be measured and this should be monitored for the duration of aciclovir treatment. See Appendix 2 for safe usage of aciclovir.

Duration of treatment
HSV PCR positive cases should be given a minimum of 21 days of IV acyclovir, with LP at end of treatment course for repeat HSV PCR prior to stopping acyclovir. Oral aciclovir or valaciclovir are not valid alternatives.

In the case of suspected encephalitis where the cause has not been identified a minimum 10 days of IV aciclovir should be given. LP should then be repeated including repeat PCR for HSV and consider repeating EEG and neuroimaging.

If these are again normal, and there are no abnormalities on EEG or neuroimaging and the child has clinically completely recovered, the aciclovir could be stopped.

In any child who clinically has had an encephalopathy, where there is either:
- Abnormal EEG
- Abnormalities on neuroimaging
- Incomplete recovery

then aciclovir should be continued for 21 days (even if the CSF was normal).

LP should be repeated in these children and second line investigations performed.

Convalescent serology should be taken 3 weeks after the initial serology was taken in any child where the cause has not been identified.

Any cases that are not straightforward should be discussed with the Neurology team and the ID team.
It is important to document carefully any decisions made to stop or start treatment and the reasons behind them.
Neonatal encephalitis

This can be even more difficult to diagnose clinically as the symptoms can be even more non-specific. There may or may not be a history of genital herpes in mother or father, or of cold sores. Many genital infections will be asymptomatic and up to 60% of HSV meningitis there is no parental history of herpes.

A very low threshold for treating with aciclovir in an infant with fever without focus should be maintained if no other cause can be found. If aciclovir is commenced ensure that PCRs have been requested on CSF. Any infant with skin lesions suggestive of HSV should have a lumbar puncture to look for CNS disease as well as viral skin swabs for HSV. Elevated liver transaminases are an important clue for disseminated herpes simplex in neonate with fever without focus.

A positive result should prompt discreet and sensitive counseling of parents and investigations as warranted.

CSF in infants is more likely to be normal or only mildly abnormal, and PCR has been shown to be only 70% sensitive early in infection. Therefore LP should be repeated in the first week if initial results are normal.

Duration of treatment should be minimum 21 days. LP should again be repeated at the end of treatment to ensure clearance. If the virus is not cleared it should be continued. Discuss these cases with the ID team.

Once the virus has been shown to be cleared the treatment can be stopped. However neonatal HSV CNS disease has a high relapse rate. Any recurrence of skin rash should prompt a repeat LP, as should any presentations suspicious for encephalitis, and further IV aciclovir.

Research so far has not shown convincing evidence to support oral prophylaxis with oral aciclovir or valacyclovir, however some centres advise this for up to 2 years. Discuss with the ID team any cases of recurrence.

Appendix 1

Contraindications to LP

- Signs of raised intracranial pressure:- altered pupillary responses, absent Doll’s eye reflex, decerebrate or decorticate posture, abnormal respiratory pattern, papilloedema, hypertension and bradycardia
- GCS of <13 or deteriorating
- Other focal neurological signs such as hemi/monoparesis, extensor plantar responses, ocular palsies
- Recent or prolonged seizures
- Focal seizures
- Strong suspicion of meningococcal disease
- Shock
- Local superficial infection at site of LP
- Coagulation disorder

Note that a normal CT scan does not exclude raised intracranial pressure and if clinical concerns remain, do not proceed.
Appendix 2

Dosing regime for aciclovir

- Neonates and infants up to 3 months
  20mg/kg/dose 8 hourly

- Children 3 months to 12 years
  500mg/m²/dose 8 hourly

- 12 years and over
  10mg/kg/dose 8 hourly

Toxic to veins so a central venous catheter is advised for long courses.
Check baseline renal function and monitor frequently.
Avoid using in conjunction with ceftriaxone as this can increase the chance of renotoxicity.

Appendix 3

Lab guide (see www.labplus.co.nz for additional info)

- Plasma
  - Lactate grey on ice
  - Pyruvate on ice
  - Ammonia purple on ice
  - Amino acids green on ice
  - Copper/ceruloplasmin
  - Lead
  - All immune mediated tests except antiNMDAR

- CSF lactate, pyruvate and amino acids also need to go on ice

References

The role of lumbar puncture in suspected CNS infection. R Kneen, T Solomon, R Appleton. Arch Dis Child 2002;87:181-183


Encephalitis clinical guidelines, Great Ormond Street Hospital. www.ich.ucl.ac.uk/clinical_information/clinical_guidelines/cmg_guideline_00031