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Management of Suspected Viral Encephalitis in Children

Professional Guidelines

Association of British Neurologists and British Paediatric Allergy,
Immunology and Infectious Diseases Group National Guidelines

Summary document produced on behalf of the National Encephalitis
Guidelines Development Group and the Encephalitis Society

Management of Suspected Viral Encephalitis in Children.

This is a synopsis produced for The Encephalitis Society. To read the full article please see: Kneen R, Michael BD, Menson E, Mehta B, Easton A, Hemingway C, Klapper PE, Vincent A, Lim M, Carrol E, Solomon T. On behalf of the National Encephalitis Guidelines Development and Stakeholder Groups. Management of suspected viral Encephalitis in children: Association of British Neurologists and British Paediatric Allergy, Immunology and Infectious Diseases Group National Guidelines. **Journal of Infection** 2012; 64(5): 449-477.

A separate parallel document has been produced for adults: see page 15.

1. Introduction

Encephalitis is defined as a syndrome of neurological dysfunction caused by inflammation of the brain parenchyma. Although Encephalitis in childhood is relatively rare, its importance lies in the fact that for many forms, treatment is effective if started promptly: in contrast, delays in treatment can be devastating. Encephalitis has many causes and some are specific to childhood. Those who ultimately have a proven diagnosis of Encephalitis are uncommon, but many children will present with symptoms and signs suggestive of Encephalitis so it is crucial that front line health care professionals should be aware of how to recognise and manage these children. Strictly speaking, inflammation of the brain parenchyma is a pathological diagnosis, however due to the practical limitations of this, surrogate clinical markers of inflammation are usually used including the results of CSF analysis and brain imaging findings.

Classification of Encephalitis

Encephalitis can be caused by many individual disease processes but can broadly be divided into those associated with infection (either directly or indirectly) and non-infectious causes. Direct infections of the Cranial Nervous System (CNS) can be caused by many viruses, bacteria (especially intracellular bacteria such as *Mycoplasma pneumoniae*), parasites and fungi. Those indirectly associated with infection include an acute demyelinating process, which is often temporally related to a prior infection outside of the CNS. This process may also follow immunisation and is known as Acute Disseminated Encephalomyelitis (ADEM). Non-infectious causes include antibody-mediated Encephalitis, which is may or may not be paraneoplastic¹. Most viral Encephalitides are acute, but sub-acute or chronic presentations are characteristic of particular pathogens, especially in the immunocompromised

Epidemiology

The incidence of Encephalitis in children is difficult to establish as reported studies have used different case definitions, methodologies and different geographic locations and study populations. However, in western settings reported incidences range from 6.3-7.4 per 100,000 for all ages (adults and children) and approximately 10.5-13.8 per 100,000 children.² In the UK, this should equate to 1-2 children per year in a typical district general hospital and 8-10 in a large tertiary children's hospital.

In industrialised nations, the most commonly diagnosed cause of Encephalitis is Herpes Simplex Virus (HSV) with an annual incidence of 1 in 250,000 to 500,000.³ The age specific incidence is bimodal, with peaks in childhood and the elderly. Most HSV Encephalitis is due to HSV type 1 but about 10% is due to HSV type 2. The latter occurs typically in immunocompromised adults and in neonates in whom it can also cause a disseminated infection. Varicella Zoster Virus (VZV) is also a relatively common cause of viral Encephalitis, especially in the immunocompromised, whilst Cytomegalovirus (CMV) occurs almost exclusively in this group. Enteroviruses most often cause aseptic meningitis but can also be an important cause of Encephalitis. Among the other non-infectious causes of Encephalitis, immune mediated conditions are increasingly being recognised including ADEM and Encephalitis associated with antibodies to the voltage-gated potassium channel complex, or N-methyl-D-aspartate antibody (NMDA) receptors.^{1,4}

Aims and Scope of this Guideline

In the 1980s the outcome of HSV Encephalitis in adults was shown to be dramatically improved by aciclovir treatment.^{5,6} Delays in starting treatment, particularly beyond 48 hours after hospital admission, are associated with a worse prognosis.^{7,8} Several comprehensive reviews of the investigation and management of Encephalitis have been published,⁹⁻¹¹ but their impact on day-to-day clinical practice appears to be limited.¹²⁻¹⁴ The emergency management of meningitis in children and adults was revolutionised by the introduction of a simple algorithm as part of management guidelines.¹⁵⁻¹⁷

In February 2008 a group of clinicians met in Liverpool to begin the development process for clinical care guidelines based around a similar simple algorithm (See pages 14,15 - Algorithm for the Management of Suspected Viral Encephalitis), supported by an evidence base, whose implementation, it is hoped, would improve the management of patients with suspected Encephalitis.

The scope of the guideline is to cover the initial management of all children with *suspected* Encephalitis, up to the point of diagnosis and early treatment, in an acute care setting such as acute medical unit or emergency room. They are thus intended as a ready reference for clinicians encountering the more common causes of Encephalitis, rather than specialists managing rarer causes. The guidelines also cover the specific treatments and further management of patients for whom a diagnosis of viral Encephalitis is made, particularly that due to HSV, VZV and enteroviruses. Encephalitis due to CMV is almost exclusively seen in the immunocompromised and is not covered in detail; its diagnosis and management is covered in HIV guidelines.¹⁸ At the end of the guidelines the special circumstances of returned travellers, immunocompromised patients and Encephalitis associated with antibodies are discussed.

Many patients with suspected viral Encephalitis ultimately prove to have another infectious or non-infectious cause for their illness. The further management and treatment of such patients is beyond the scope of this guideline, but we have included a section on follow-up and support for patients with Encephalitis in both the healthcare and voluntary sectors after discharge from hospital. Finally, we have included some suggestions for audit standards to assess practice before and after implementation of the guidelines.

Definition of childhood for this document

This guideline is for the management of suspected viral Encephalitis in children aged older than 28 days (outside the neonatal period) and younger than 16 years. The management of neonatal Encephalitis (including premature infants) is outside the scope of this document.

Methods

The contribution from the various sections were assimilated in accordance with the AGREE (appraisal of guideline research and evaluation) collaboration¹⁹. The GRADE approach was used for rating the strength of evidence (recommendations rated A to D and quality of evidence supporting the evidence is rated from I to III)²⁰



2. Diagnosing Encephalitis

Which clinical features should lead to a suspicion of Encephalitis in children, how do they differ from other encephalopathies, and can they be used to diagnose the underlying cause?

Recommendations

- The constellation of a current or recent febrile illness with altered behaviour, cognition or consciousness or new onset seizures or new focal neurological signs should raise the possibility of Encephalitis, or another CNS infection, and should trigger appropriate investigations (A, II)
- The differential diagnosis of encephalopathy (due to metabolic, toxic, autoimmune causes or sepsis outside the CNS) should be considered early (B, III), especially if there are features suggestive of a non-encephalitic process, such as a past history of similar episodes, symmetrical neurological findings, myoclonus, clinical signs of liver failure, a lack of fever, acidosis or alkalosis (B, III)
- Patients presenting with a sub-acute (weeks to months) Encephalitis should trigger a search for autoimmune, paraneoplastic, metabolic aetiologies (C, III)
- The priority of the investigations shown in Table 9 is determined by the patient's clinical history and clinical presentation (C, III)

Which patients with suspected Encephalitis should have a lumbar puncture (LP), and in which should this be preceded by a computed tomography (CT) scan?

Recommendations

- All patients with suspected Encephalitis should have a lumbar puncture as soon as possible after hospital admission, unless there is a clinical contraindication (Table 10. Contraindications to immediate lumbar puncture) (A, II)
- Clinical assessment and not cranial CT should be used to determine if it is safe to perform a LP (A, II)
- If there is a clinical contraindication indicating possible raised intracranial pressure due to or causing brain shift, a CT scan should be performed as soon as possible, (A, II). An immediate LP following this should ideally be considered on a case by case basis, unless the imaging reveals significant brain shift or tight basal cisterns due to or causing raised ICP, or an alternative diagnosis, or the child's clinical condition changes (B, III)
- If an immediate CT is not indicated, imaging (CT or, preferably, MRI) should be performed as soon as possible after the LP (A, II)
- In anticoagulated patients, adequate reversal (with protamine for those on heparin and vitamin K, prothrombin complex concentrate, or fresh frozen plasma for those on warfarin) is mandatory before lumbar puncture (A, II). In patients with bleeding disorders, replacement therapy is indicated (B, II). If unclear how to proceed, advice should be sought from a haematologist (B, III)
- In situations where an LP is not possible at first, the situation should be reviewed every 24 hours, and an LP performed when it is safe to do so (B, II)

- If an initial LP is non-diagnostic, a second LP should be performed 24-48 hours later (B, II)
- Children and young adults should be stabilised before performing a CT scan, and an anaesthetist, paediatrician or intensivist should be consulted (A, III)
- Lumbar punctures should be performed with needles that meet the standards set out by the National Patient Safety Agency (A, III)

What information should be gathered from the LP?

Recommendations

- Cerebrospinal Fluid (CSF) investigations should include:
 - Opening pressure when possible (A, II)
 - Total and differential white cell count, red cell count, microscopy, culture and sensitivities for bacteria (A, II)
 - If necessary, the white cell count and protein should be corrected for a bloody tap
 - Protein, lactate and glucose, which should be compared with a plasma glucose taken just before the LP (A, II)
 - A sample should be sent and stored for virological investigations or other future investigation as indicated in the next section (A, II)
 - Culture for *Mycobacterium tuberculosis* when clinically indicated (A, II)
- If there is a strong clinical diagnosis of Encephalitis in a child, but the initial CSF results are normal, a second LP should be undertaken and all CSF tests repeated, including consideration for antibody detection (A, II)

What virological investigations should be performed?

Recommendations

- All patients with suspected Encephalitis should have a CSF PCR test for HSV (1 and 2), VZV and enteroviruses as this will identify 90% of known viral cases and EBV considered (B, II)
- Further testing should be directed towards specific pathogens as guided by the clinical features such as travel history and animal or insect contact (B, III)

What antibody testing should be done on serum and CSF?

Recommendations

- Guidance from microbiological/virological or infectious disease specialists should be sought in deciding on these investigations (B, III)
- In patients with suspected Encephalitis where PCR of the CSF was not performed acutely, a later CSF sample (at approximately 10-14 days after illness onset) should be sent for HSV specific IgG antibody testing (B, III)
- In suspected flavivirus Encephalitis CSF should be tested for IgM antibody (B, II)
- Acute and convalescent blood samples should be taken as an adjunct to diagnostic investigation especially when EBV, arboviruses, Lyme disease, cat scratch disease, rickettsiosis or ehrlichiosis are suspected (B, II)

What PCR/culture should be done on other samples (e.g. throat swab, stool, vesicle etc)?

Recommendations

- Investigation should be undertaken through close collaboration between a laboratory specialist in microbiology, virology, infectious diseases and the clinical team (B, III)
- In all patients with suspected viral Encephalitis throat and rectal swabs for enterovirus investigations should be considered (B, II); and swabs should also be sent from vesicles, if present
- When there is a recent or concomitant respiratory tract infection, throat swab or sputum/lavage should be sent for PCR for respiratory viruses (B, II)
- When there is suspicion of mumps CSF PCR should be performed for this and parotid gland duct or buccal swabs should be sent for viral culture or PCR (B, II)

Which children with Encephalitis should have a HIV test?

Recommendations

- We recommend that an HIV test be performed on all patients with Encephalitis, or with suspected Encephalitis irrespective of apparent risk factors (A, II)

What is the role of brain biopsy in children with suspected viral Encephalitis?

Recommendations

- Brain biopsy has no place in the initial assessment of suspected acute viral Encephalitis in immunocompetent children. Stereotactic brain biopsy should be considered in a child with suspected Encephalitis in whom no diagnosis has been made after the first week, especially if there are focal abnormalities on imaging and if the findings could change the child's management (B, II)
- If imaging shows nothing focal, an open biopsy, usually from the non-dominant frontal lobe, may be preferable (B, II)
- The biopsy should be performed by an experienced paediatric neurosurgeon and the histology should be examined by an experienced neuropathologist (B, III)



What is the role of magnetic resonance imaging (MRI) and other advanced imaging techniques in children with suspected viral Encephalitis?

Recommendations

- MRI (including diffusion weighted imaging), should be performed as soon as possible on all patients with suspected Encephalitis in whom the diagnosis is uncertain; ideally this should be within 24 hours of hospital admission, but certainly within 48 hours (B, II). Where the patient's clinical condition precludes an MRI, urgent CT scanning may reveal an alternative diagnosis (A, II)
- MRI sequences obtained need to be chosen appropriately for a paediatric population and images should be interpreted by an experienced paediatric neuroradiologist (B, II)
- The role of MR spectroscopy is uncertain; SPECT and PET are not indicated in the assessment of suspected acute viral Encephalitis (B, II)



Which children with suspected viral Encephalitis should have an electroencephalogram (EEG)?

Recommendations

- An EEG should not be performed routinely in all patients with suspected Encephalitis; however, in patients with mildly altered behaviour, if it is uncertain whether there is a psychiatric or organic cause an EEG should be performed to establish whether there are encephalopathic changes (B, II)
- EEG should also be performed if subtle motor, or subclinical seizures are suspected (B,II)
- An EEG should be performed in children with suspected chronic viral Encephalitis for example SSPE (B, II)

3. Treatment of Viral Encephalitis

For which patients should aciclovir treatment be started empirically?

Recommendations

- Children with suspected Encephalitis should have intravenous aciclovir started if the initial CSF and/or imaging findings suggest viral Encephalitis, and definitely within 6 hours of admission if these results are awaited (A, II)
- If the first CSF microscopy or imaging is normal but the clinical suspicion of HSV or VZV Encephalitis remains, aciclovir should still be started within 6 hours of admission whilst further diagnostic investigations (as outlined below) are awaited (A, II)
- The dose of intravenous aciclovir should be:
 - 3 months-12 years 500mg/m² 8 hourly
 - >12 years 10mg/kg 8 hourly
- The dose of aciclovir should be reduced in patients with pre-existing renal impairment (A, II)
- Patients with suspected Encephalitis due to infection should be notified to the appropriate Consultant in Communicable Disease Control (In Scotland, only patients with a proven aetiology or those occurring as part of an unusual outbreak are notifiable) (A, III)
- If meningitis is also suspected, the child should also be treated in accordance with the NICE meningitis guideline (A, II)

How long should aciclovir be continued in proven HSV Encephalitis, and is there a role for oral treatment?

Recommendations

- In children with proven HSV Encephalitis, intravenous aciclovir treatment should be continued for 14-21 days (A, II), and a repeat LP considered at this time to confirm the CSF is negative for HSV by PCR (B, II); particularly if there are concerns that the treatment is ineffective (severe disease, immune-compromise, previous relapses)
- If the CSF is still positive for HSV by PCR, aciclovir should continue, with weekly CSF PCR until it is negative (B, II)
- In children aged 3 months-12 years a minimum of 21 days of aciclovir should be given before repeating the LP (B, III)

When can presumptive treatment with aciclovir be safely stopped, in patients that are HSV PCR negative?

Recommendations

- Aciclovir can be stopped in an immunocompetent child, if
 - An alternative diagnosis has been made, or
 - HSV PCR in the CSF is negative on two occasions 24-48 hours apart, and MRI imaging (performed >72 hours after symptom onset), is not characteristic for HSV Encephalitis, or
 - HSV PCR in the CSF is negative once >72 hours after neurological symptom onset, with normal level of consciousness, normal MRI (performed >72 hours after symptom onset), and a CSF white cell count of less than 5/mm³ (B, III)

What is the role of corticosteroids in HSV Encephalitis?

Recommendations

- Whilst awaiting the results of a randomised placebo-controlled trial corticosteroids should not be used routinely in patients with HSV Encephalitis (B, III)
- Corticosteroids may have a role in patients with HSV Encephalitis under specialist supervision, but data establishing this are needed and the results of a prospective RCT are awaited (C, III)

What should be the specific management of VZV Encephalitis?

Recommendations

- No specific treatment is needed for VZV cerebellitis (B, II).
- For VZV Encephalitis, whether a primary infection or a reactivation, intravenous aciclovir 500mg/m² or 10-15mg/kg three times daily is recommended (B, II);
- If there is a vasculopathy (i.e. stroke), there is a case for using corticosteroids (B, II)

What should be the specific management of enterovirus meningoencephalitis?

Recommendations

- No specific treatment is recommended for enterovirus Encephalitis; in patients with severe disease pleconaril (if available) or intravenous immunoglobulin may be worth considering (C, III)

What acute facilities should be available and which patients should be transferred to a specialist unit?

Recommendations

- Patients with suspected acute Encephalitis should have access to a paediatric neurological specialist opinion and should be seen as soon as possible and definitely within 24 hours of referral (B, III)
- There should be access to neuroimaging (both MRI and CT), under general anaesthetic if needed, and neurophysiology (EEG), which may mean transfer to a specialist paediatric neuroscience unit (B, III)
- As CSF diagnostic assays are critical to confirming diagnosis, the results of CSF PCR assays should be available within 24-48 hours of a lumbar puncture being performed. (B, III)
- When a diagnosis is not rapidly established or a patient fails to improve with therapy, transfer to a paediatric neurological unit is recommended. The transfer should occur as soon as possible and definitely within 24 hours of being requested (B, III)
- Patients with falling level of consciousness require urgent assessment by paediatric Intensive Care Unit staff for airway protection and ventilatory support, management of raised intracranial pressure, optimisation of cerebral perfusion pressure and correction of electrolyte imbalances. (A, III)

What rehabilitation and support services should be available for children affected by Encephalitis and their families?

Recommendations

- Parents and older children (where their cognitive ability permits) should be made aware of the support provided by voluntary sector partners such as The Encephalitis Society (www.encephalitis.info) (B, II)
- At the time of discharge, children should have either a definite or suspected diagnosis. Arrangements for outpatient follow-up and plans for on-going therapy and/or rehabilitation should be formulated at a discharge meeting (A, III)
- All children should have access to assessment for rehabilitation (A, III)



4. Special Circumstances

What is the management of suspected Encephalitis in children returning from travelling overseas?

Recommendations

- Patients returning from malaria endemic areas should have rapid blood malaria antigen tests and ideally three thick and thin blood films examined for malaria parasites (A, II). Thrombocytopenia, or malaria pigment in neutrophils and monocytes may be a clue to malaria, even if the films are negative
- If cerebral malaria seems likely, and there will be a delay in obtaining the malaria film result, anti-malarial treatment should be considered and specialist advice obtained (A, III)
- The advice of the regional paediatric infectious diseases, and paediatric neuroscience units should be sought regarding appropriate investigations and treatment for the other possible causes of Encephalitis in a returning traveller (Table 2) (B, III)

What differences are there in the management of suspected Encephalitis in the immunocompromised?

Recommendations

- Encephalitis should be considered in immunocompromised patients with altered mental status, even if the history is prolonged, the clinical features are subtle, or there is no febrile element (A, III)
- In patients with known severe immunocompromise a CT scan before LP should be considered (B, III). If a patient's immune status is not known, there is no need to await the result of an HIV test before performing a LP
- MRI should be performed as soon as possible in all patients (A, II)
- Diagnostic microbiological investigations for all immunocompromised patients with suspected CNS infections include (B, II):
 - CSF PCR for HSV 1 & 2, VZV and enteroviruses
 - CSF PCR for EBV, and CMV
 - CSF acid fast bacillus staining and culture for *Mycobacterium tuberculosis*
 - CSF and blood culture for *Listeria monocytogenes*
 - Indian ink staining and/or cryptococcal antigen (CRAG) testing of CSF and serum for *Cryptococcus neoformans*
 - Antibody testing of serum and if positive CSF PCR for *Toxoplasma gondii*
 - Antibody testing of serum and if positive CSF for syphilis (B, II)

Other investigations to consider, depending on the circumstances, include (C, III):

- CSF PCR for HHV6 and 7
- Parvovirus B19
- Measles
- West Nile virus Encephalitis
- CSF PCR for JC/BK virus
- CSF examination for *Coccidioides* species, and *Histoplasma* species

- Children with HIV suffering from severe infections or other complex problems should be treated in a regional hub or London Lead Centre (A,II)
- Immunocompromised patients with Encephalitis caused by HSV-1 or 2, should be treated with intravenous aciclovir (10mg/kg three times daily) for at least 21 days, and reassessed with a CSF PCR assay; following this long term oral treatment should be considered until the CD count is $>200 \times 10^6/L$, or if CD4%, 15% if <5 years old (A, II)
- Acute concomitant VZV infection causing Encephalitis should be treated with intravenous aciclovir (A, II)
- CNS CMV infections should be treated with ganciclovir, foscarnet or cidofovir (A, II)
- Children with VZV Encephalitis should be treated with intravenous acyclovir $500\text{mg}/\text{m}^2$ for at least 10 days, although immunocompromised children may require longer treatment (B, III)

What differences are there in the presentation and management of Encephalitis associated with antibodies?

Recommendations

- Antibody-mediated Encephalitis should be considered in all patients with suspected Encephalitis as they have a poorer outcome if untreated. Moreover the clinical phenotypes of these recently described disorders are still expanding (B, III)
- Clinical features, such as limbic Encephalitis, a sub-acute presentation, speech and movement disorders and intractable seizures may suggest an antibody-mediated Encephalitis, although these features are not exclusive to antibody-mediated disease (B, III)
- Although tumours occur less frequently in children, all patients with proven VGKC or NMDAR-associated Encephalitis should have screening for neoplasm (C, III), and extended surveillance for several years (C, III)
- Annual tumour screening should be conducted in patients with NMDAR antibody associated Encephalitis if no tumour has been found, especially if the patient has a poor response to therapy or there are relapses (B, III)
- Early immune suppression and tumour removal should be undertaken when possible (B, III)

Guideline implementation and audit

We have included a table (see full published guidelines) of suggested clinical and operational issues that are relatively easy to audit in a standardised manner, and which can be adapted for local use.



Acknowledgements

Rachel Kneen, Benedict Michael, Esse Menson, Bimal Mehta, Ava Easton, Cheryl Hemingway, Paul Klapper, Angela Vincent, Ming Lim, Enitan Carrol, Tom Solomon.

In addition to the authors listed, the following are currently members of the National Encephalitis Guidelines Development Group: *Phil Smith, Nick Davies, Frances Sanderson, Ian Hart, Nick Beeching, Mark Holland, Camilla Buckley, Solomon Almond, Peter Burnham, Mehrengise Cooper, Jean-Pierre Lin, Hermione Lyall, Kevin Mackway-Jones, Nick Makwana, Anthony Marson, Isam Osman, Andrew Riordan, Delane Shingadia, Aman Sohal, David Stoeter, Edmund Wilkins.*

This article presents independent work funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference Number RP-PG-0108-10048). Additional funding was provided by the Association of British Neurologists, the British Infection Association, The Encephalitis Society and the University of Liverpool; these organisations contributed members to the guideline development team, but have no conflicts of interests to declare.

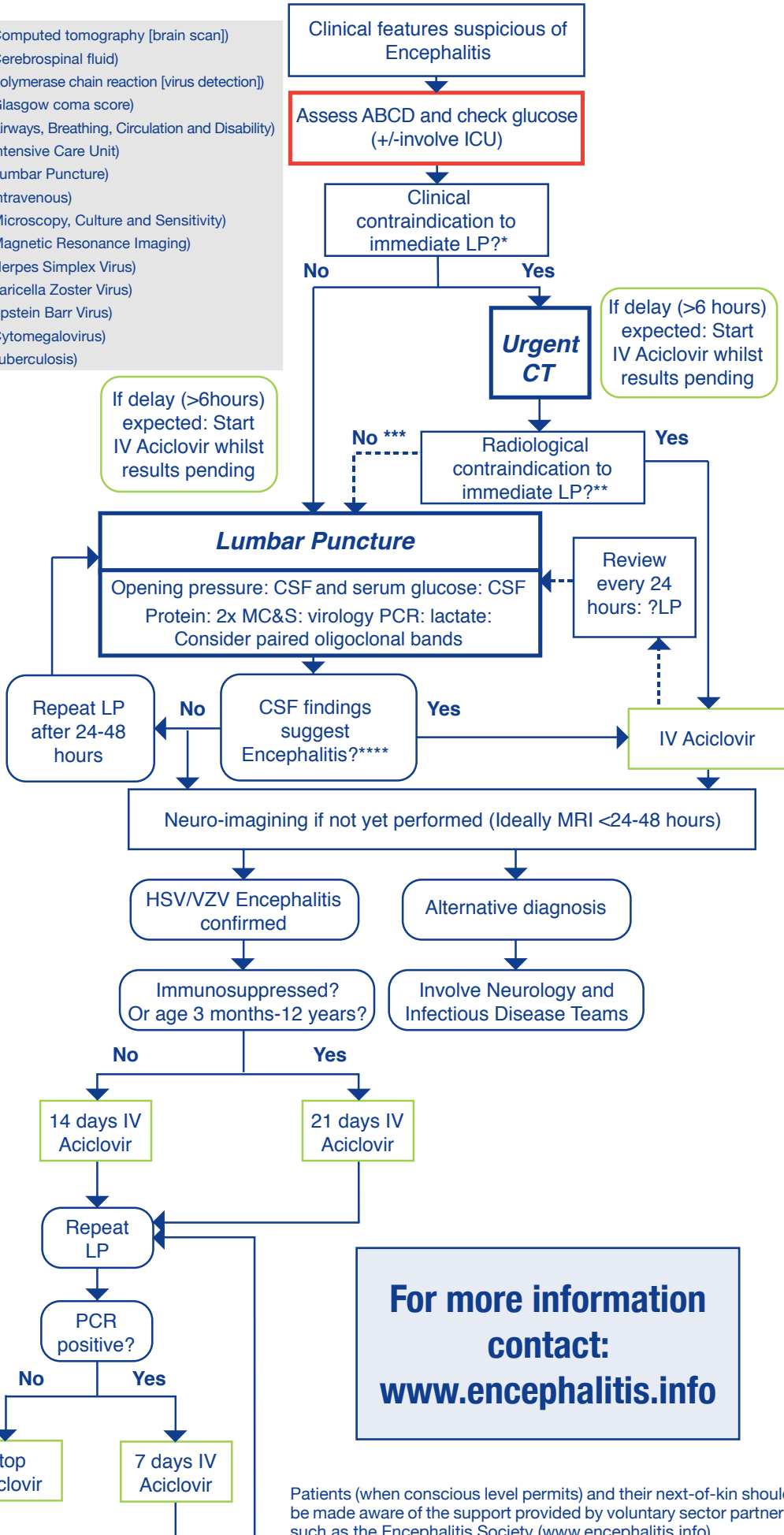
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The Management of suspected viral Encephalitis

KEY:

CT	(Computed tomography [brain scan])
CSF	(Cerebrospinal fluid)
PCR	(Polymerase chain reaction [virus detection])
GCS	(Glasgow coma score)
ABCD	(Airways, Breathing, Circulation and Disability)
ICU	(Intensive Care Unit)
LP	(Lumbar Puncture)
IV	(Intravenous)
MC&S	(Microscopy, Culture and Sensitivity)
MRI	(Magnetic Resonance Imaging)
HSV	(Herpes Simplex Virus)
VZV	(Varicella Zoster Virus)
EBV	(Epstein Barr Virus)
CMV	(Cytomegalovirus)
TB	(Tuberculosis)



Additional Investigations

Consider swab

- Throat
- Rectal
- Vesicle (if present)

Sputum (if symptoms)
Urine (if mumps)

If travel consider

- 3x thick/thin malaria films
- Rapid malaria antigen test
- CSF flavivirus igM

HIV (all patients)

If positive:

- CSF PCR for EBV + CMV
- CSF TB staining + culture
- CSF + blood culture for Listeria monocytogenes
- CSF india ink staining +/- cryptococcal antigen for Cryptococcus neoformans
- CSF PCR + serology for Toxoplasma gondii
- CSF + serum antibody for syphilis

Consider:

- CSF PCR for HHV6 + 7
- CSF PCR for JC/BK virus
- CSF for Coccidioides + Histoplasma

If CSF HSV PCR not sent

(on first LP)

- Repeat CSF PCR on 2nd LP
- Consider HSV CSF IgG at 10-14 days

EEG Indications

- If subtle motor status epilepticus suspected
- If unclear if psychiatric cause or encephalopathy

Involve

- Microbiology
- Virology
- Infectious Diseases
- Neurology

Aciclovir Dose:

(adjust for renal failure)

Given 8 hourly:
Neonate-3 months: 20mg/kg
3 months-12 years: 500mg/m²
>12 years: 10mg/kg

Reference:

Journal of Infection
2012; 64(4):347-73

* } Tables associated with
** } this algorithm are on
*** } the next page.
**** }

Patients (when conscious level permits) and their next-of-kin should be made aware of the support provided by voluntary sector partners such as the Encephalitis Society (www.encephalitis.info)

*** Clinical contraindications to lumbar puncture without neuro-imaging**

- Moderate-severe impairment of consciousness: Reduced or fluctuating GCS<13 or fall >2
- Focal neurological signs (e.g. unequal, dilated or poorly responsive pupils)
- Abnormal posture or posturing
- Papilloedema
- After seizures until stabilised
- Relative bradycardia with hypertension
- Abnormal 'doll's eye' movements
- Immunocompromise
- Systemic shock
- Coagulation abnormalities:
 - Results (if obtained) outside the normal range
 - Platelet count <100x10⁹ /L
 - Anticoagulant therapy
- Local infection at lumbar puncture site
- Respiratory insufficiency
- Suspected meningococcal septicaemia

Tables associated with the algorithm on page 14

**** Radiological Contraindications to LP**

- Significant brain shift/swelling
- Tight basal cisterns
- Alternative diagnosis made

Many patients will need a CT before a LP, because of their clinical contraindications to an immediate LP; such patients should have a CT, and then ideally a LP should be considered on a case by case basis (if still indicated and no radiological contraindications are identified) within 6 hours.

****** CSF Interpretation**

Investigation	Normal	Bacterial	Viral	Tuberculous	Fungal
Opening pressure	10-20cm	Highly Cloudy	Normal/high	High	High/very high
Colour	Clear	Cloudy	"Gin" clear	Cloudy/yellow	Clear/cloudy
Cells	<5	High/very high 100-50000	Slightly increased 5-1000	Slightly increased <500	Normal-high 0-1000
Differential	Lymphocytes	Neutrophils	Lymphocytes	Lymphocytes	Lymphocytes
CSF/Plasma Glucose	50-66%	Low<40%	Normal	Low-very low (30%)	Normal-low
Protein (g/l)	<0.45	High >1	Normal-high 0.5-1	High-very high 1.0-5.0	Normal-high 0.2-5.0

GRADE rating system for the strength of the guidelines recommendations and the quality of the evidence.

Strength of recommendation		Quality of evidence	
A	Strongly recommended	I	Evidence from randomised controlled trials
B	Recommended, but other alternatives may be acceptable	II	Evidence from non-randomised studies
C	Weakly recommended: seek alternatives	III	Expert opinion only
D	Never recommended		

Atkins D, Best D, Briss P A, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004; 328: 1490.

References:

Solomon T, Michael BD (joint first), et al. On behalf of the National Encephalitis Guidelines Development Group. Management of suspected viral Encephalitis in adults: Association of British Neurologists and British Infection Association National Guideline. *Journal of Infection* 2012; 64(4):347-73. If you would like to read the article in full, it is available on the following website:

[www.journalofinfection.com/article/S0163-4453\(11\)00563-9/fulltext](http://www.journalofinfection.com/article/S0163-4453(11)00563-9/fulltext)

Kneen R, Michael BD (joint first), et al. On behalf of the National Encephalitis Guidelines Development Group. Management of suspected viral Encephalitis in children: Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group National Guideline. *Journal of Infection* 2012; 64(5):449-77. If you would like to read the article in full, it is available on the following website:

[www.journalofinfection.com/article/S0163-4453\(11\)00562-7/fulltext](http://www.journalofinfection.com/article/S0163-4453(11)00562-7/fulltext)

ENCEPH UK

Understanding and Improving the Outcome of Encephalitis

In this NIHR Programme Grants for Applied Research award led by Professor Tom Solomon at the Institute of Infection and Global Health, at the University of Liverpool, over the next five years we will:

- Study the clinical predictors of Encephalitis, and of poor outcome
- Better understand those outcomes in terms of cognitive function, quality of life, and cost
- Develop the means of intervening to improve the outcome, including implementation of these guidelines.

Studies

This programme grant consists of a series of inter-related studies; a retrospective study looking back at previous patients, a prospective study investigating new patients and an Intervention study to change practice; the over-arching aim is to better understand and improve the outcomes of Encephalitis for the benefit of patients.

The research will be based around three patient populations:

- A cohort of patients who had Encephalitis previously, who were recruited between 2005 and 2008 during the Department of Health-funded Health Protection Agency study of the Aetiology of Encephalitis in England (the HPA cohort)
- A new large 4-year multi-centre prospective cohort study of adults and children with suspected Encephalitis across the UK which will recruit in 60 hospitals. The paediatric arm of this study is a collaborative study called the Childhood Meningitis & Encephalitis Study (ChiMES). It is jointly led by Professor Andrew Pollard from the Oxford Vaccine Group.
- Patients with suspected Encephalitis, on whom data will be collected through a cluster randomised controlled trial of implementation of these guidelines which will be conducted in 20 hospitals.

For more information and to get involved visit:

www.encephuk.org



ENCEPHALITIS
SOCIETY

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