Encephalitis in Children

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Encephalitis in Children

Definition

Epidemiology

Etiology

Management
15y old boy

- 2d history with confusion, amnesia and jerks in legs
- 2y ago in Kenia, spent afternoon with a stranger
- no focals signs on examination, no fever
- Bloods and LP normal
- EEG with frontal slowing
Possible Causes?

- Toxic
- Antibody related
- Meningitis
- Acute Demyelination
- Epilepsy
- Vascular
- Encephalitis
- Metabolic
- Other
- Tumor
Encephalitis - Definition

Inflammatory process of the brain with clinical evidence of neurological dysfunction

1. **Major Criterion**: Altered mental status (decreased level of consciousness, lethargy, personality changes) > 24h, no alternative explanation

2. **Minor Criteria**: Evidence of inflammation with:
   - fever within 72 hours before presentation
   - seizures
   - focal neurological deficit
   - inflammation on neuroimaging
   - CSF pleocytosis
   - EEG changes consistent with encephalitis

   **2 possible, 3 or more probable/confirmed**

Conditions Mimicking Encephalitis

**Vascular**
- Acute ischaemic stroke
- Venous sinus thrombosis

**Metabolic**
- Ketoacidosis
- Fluid/electrolyte dist.
- Hepatic encephalopathy
- Haemolytic Uremic Syndrome
- Reye Syndrome

**Toxic**
- Drugs, alcohol
- Poisoning (smoke inh. etc.)

**Epileptic**
- post-ictal state
- non-convulsive status epileptics

**Neoplastic**
- Brain tumors
- Metastasis
- Paraneoplastic

**Others**
- psychogenic symptoms
- head trauma
- Complex febrile convulsions
# Encephalitis - Infectious Etiology

<table>
<thead>
<tr>
<th>Virus</th>
<th>Bacteria</th>
<th>Rickettsiaeae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes viruses</td>
<td>Bacterial Meningitis</td>
<td>Cat-scratch disease</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>Tuberculosis</td>
<td>Q-fever</td>
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<tr>
<td>Arbovirus</td>
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<tr>
<td>Paramyxovirus</td>
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<table>
<thead>
<tr>
<th>Parasites</th>
<th>Fungi</th>
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<tbody>
<tr>
<td>Malaria</td>
<td>Cryptococcus</td>
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<tr>
<td>Toxoplasma</td>
<td>Blastomyces</td>
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<tr>
<td>Cysticercosis</td>
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<td>...</td>
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Encephalitis - Non-Infectious

**Etiology**

**Post/para infectious**
- Acute Dissiminated Encephalomyelitis (ADEM)
- Guillain Barré Syndrome

**Autoimmune**
- NMDA receptor
- Voltage gated potassium channel

**Paraneoplastic**
- NMDA receptor
- Limbic encephalitis

**Vasculitis**
- SLE
- Polyarteritis nodosa
- ANCA associated
Encephalitis - Incidence

- Incidence 3.5-7.4/100.00 worldwide
- 16/100.000 in children
- UK 1.5/100.00, 2.8/100.000 in children
Etiology of Encephalitis
Galanikis et al, 2009, 42 children in Greece

- Unknown: 43%
- Enterovirus: 14%
- Herpes sp.: 24%
- Others: 19%
Etiology of Encephalitis in France
Maille et al 2008, 253 patients (adults and children)

- unknown: 48%
- Enterovirus: 1%
- HSV1: 22%
- VZV: 8%
- M. tuberculosis: 8%
- L. monocytogenes: 5%
- Others: 8%
Etiology of Viral encephalitis in Vietnam
Le et al 2010, 194 children < 16y

- JEV: 26%
- Dengue: 59%
- Entero: 9%
- Unknown: 9%
Etiology of Encephalitis in the UK
Granerod 2010, 203 pt., median 30y
confirmed infection in 86 pt (42%)
4 year old boy
• Right sided hemiparesis, initially intermittent
• 6 months after chickenpox
• LP with positive VZV PCR, normal cell count

Tentative diagnosis:
Varicella zoster associated cerebral vasculitis
Varicella Zoster Virus - Neurological Complications

- 2nd most common sporadic encephalitis after HSV
- Encephalitis during primary infection or immunocompromised patients
- VZV only virus with affinity to CSV blood vessels, leading cause of childhood stroke - **VZV vasculopathy**
- Zoster: **postherpetic neuralgia, peripheral neuropathy**
- **Cerebellar ataxia** during acute illness, probably parainfectious demyelinating leukoencephalopathy
- **Myelitis**
- Adenovirus
- Arboviruses
- Encephalomyocarditis virus
- Enteroviruses
- Hepatitis A, B
- Herpesvirus (HSV) group
  - HSV 1 and 2
  - Varicella-zoster virus
  - Epstein-Barr virus
  - Cytomegalovirus
  - Human herpesvirus 6
  - Herpesvirus B
- Influenza
- Lymphocytic choriomeningitis virus
- Measles
- Mumps
- Parainfluenza
- Parvovirus
- Rabies
- Rotavirus
- Respiratory syncytial virus
- Rubella
- Smallpox
- Vesicular stomatitis virus
Geographically restricted (arboviral except Rabies and Nipah)

**Africa**
West Nile, Rift Valley, Dengue, rabies, Crimean-Congo hemorrhagic fever

**Americas**
West Nile, Rabies, St Louis, La Crosse, Dengue

**Asia**
Japanese, West Nile, Dengue, Rabies, Nipah

**Australia**
Murray Valley, Japanese

**Europe and Middle East**
West Nile, rabies, tick-borne encephalitis
Herpes Simplex Virus Encephalitis

- most common cause of infectious sporadic encephalitis, est. 500,000/year worldwide, 31-50% children
- 90% caused by HSV1, 10% HSV2 (neonates predominant)
- 2/3 reactivation of latent infection - genetic? in children and young adults primary infection
- Symptoms: Fever, seizures (>50%), focal neurological signs
- CSF with lymphocytic pleocytosis in 75%, median 89/ microliter, normal in 13% (Scheele 2013).
- Initial PCR can be negative
-Characteristic findings on neuroimaging and EEG
Herpes Simplex Virus Encephalitis

EEG: focal or generalized slowing, focal sharp waves and spikes, PLEDs. Not characteristic for HSV

Schleede et al, 2013
# Herpes Simplex Virus Encephalitis - outcome

## Table 1.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hsieh et al.(^\text{10})</th>
<th>Elbers et al.(^\text{11})</th>
<th>Lahat et al.(^\text{16})</th>
<th>Ito et al.(^\text{17})</th>
<th>Uren et al.(^\text{30})</th>
<th>Wang et al.(^\text{79})</th>
<th>Kimura et al.(^\text{69})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal mild</td>
<td>26 (65%)</td>
<td>6 (38%)</td>
<td>16 (57%)</td>
<td>8 (33%)</td>
<td>4 (57%)</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>12 (30%)</td>
<td>5 (31%)</td>
<td>10 (36%)</td>
<td>6 (25%)</td>
<td>7 (44%)</td>
<td>2 (16%)</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Severe</td>
<td>2 (5%)</td>
<td>5 (31%)</td>
<td>0 (0%)</td>
<td>8 (33%)</td>
<td>3 (19%)</td>
<td>8 (66%)</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>2 (7%)</td>
<td>2 (8%)</td>
<td>2 (12%)</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>16</td>
<td>28</td>
<td>24</td>
<td>16</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>
Japanese Encephalitis

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Japanese Encephalitis

- Flavivirus
- 1:25-1:1000 develop encephalitis
- 67,900 cases annually, 51,000 < 14y (WHO 2011)
- 20-30% fatal, 30-50% significant neurological sequelae
- seasonal variation, infection primarily in summer months
- increased incidence and geographical distribution in the past 50 years
- vaccination effective
Japanese Encephalitis

Clinical
• Fever, headache, vomiting, decreased level of consciousness
• Parkinsonian features (hypomimia, cogwheel rigidity, tremor, pill-rolling)
• Grimacing, choreoathetosis, opisthotonus
• Brainstem features: opsoclonus, gaze palsies, pupillary changes
• Seizures, subtle or status epileptics
• Subtype with flaccid paralysis due to anterior horn cell involvement
• CSF pleocytosis 10-100/microL, mild elev. protein
Japanese Encephalitis
Table 2  Possible aetiological agents based on clinical presentation

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Possible aetiological agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial nerve abnormalities</td>
<td>HSV, EBV, listeria, tuberculous meningitis, syphilis, Lyme disease, <em>Cryptococcus neoformans</em></td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
<td>VZV, EBV, mumps virus, trypanosomiasis</td>
</tr>
<tr>
<td>Dementia</td>
<td>HIV, measles virus, syphilis, human transmissible spongiform encephalopathies</td>
</tr>
<tr>
<td>Poliomyelitis-like flaccid paralysis</td>
<td>JEV, poliovirus, enteroviruses, WNV, tick-borne encephalitis virus</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>JEV, WNV, Nipah virus</td>
</tr>
<tr>
<td>Retinitis</td>
<td>CMV, WNV, cat scratch disease, syphilis</td>
</tr>
<tr>
<td>Rash</td>
<td>VZV, HHV-6, rubella virus, typhus, syphilis, Lyme disease, WNV, HIV, enteroviruses, <em>Mycoplasma pneumoniae</em></td>
</tr>
<tr>
<td>Respiratory tract findings</td>
<td>Flu virus, adenovirus, <em>M pneumoniae</em>, <em>Mycobacterium tuberculosis</em>, Q. fever</td>
</tr>
<tr>
<td>Parotitis</td>
<td>Mumps virus</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>HIV, EBV, CMV, measles virus, rubella virus, WNV, syphilis, cat scratch disease, tuberculous meningitis, toxoplasmosis, trypanosomiasis</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Q. fever</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpes virus 6; HSV, herpes simplex virus; JEV, Japanese encephalitis virus; VZV, varicella zoster virus; WNV, West Nile virus.

from: Thompson et al, 2011
15y old boy
- 1m emotionally unstable, depressed, seen by psychiatrist
- GTCS, decreasing level of consciousness
- status epilepticus, treated on intensive care

NMDA receptor antibody encephalitis
Autoimmune Encephalitis

N-methyl-D-aspartate (anti-NMDA) receptor encephalitis

- second most common cause of immune-mediated encephalitis, 4% in UK series (Granerod 2010)
- 40% younger than 18 y
- psychiatric features, memory disturbance, speech disorder, seizures, dyskinesias, decreased level of consciousness
- associated with tumor (ovarian teratoma): 56% adult, 9% younger than 14y
- 94% abnormal CSF (increased protein, pleocytosis)
- 31% children abnormal MRI
NMDA receptor AB

from: Armangue 2012

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N-methyl-D-aspartate (anti-NMDA) receptor encephalitis

Treatment
• First-line treatment:
  High-dose steroid
  Immunoglobulin
  Plasma exchange

• Second-line treatment:
  Cyclophosphamide
  Rituximab

55% recover completely
Acute Disseminated Encephalomyelitis (ADEM)

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Acute Disseminated Encephalomyelitis (ADEM)

- Acute demyelination 1-4 wks after febrile illness, 0.8/100,000, median 6.4 yrs
- Cause: autoimmune - infection or vaccination
- Symptoms: low grade fever, encephalopathy, paresis, seizures, focal neurological signs
- CSF usually with increased white cells, values > 100 not unusual, increased protein
Acute Dissiminated Encephalomyelitis (ADEM)

Post-vaccination ADEM

- incidence 0.1-0.2/100,000 vaccinated individuals
- 5% of all ADEM cases
- primary vaccination more frequent

- Associated with several vaccines including:
  - diphtheria–tetanus–polio, smallpox, measles, mumps, rubella, Japanese B encephalitis, pertussis, influenza, hepatitis B,
- Smallpox 5/Million
- Live Measles 1-2/Million
- Japanese Encephalitis 2-20/Million, USA none in 813.00 vaccinations
Post-infectious ADEM

- Smallpox 1:400-1:4473
- Measles 1:600-1:2000
- Varicella 1:1000-1:10,000
- Rubella 1:4300-1:20,000
- Also: Mumps, Epstein-Barr virus (EBV), CMV, HSV, hepatitis A or B, Coxsackie virus, influenza A or B, HIV, HTLV-1, human herpes virus 6,
- **Bacteria**: Mycoplasma, Borrelia, Campylobacter, Leptospira, Chlamydia, Legionella, and group A beta-haemolytic streptococci
Acute Disseminated Encephalomyelitis (ADEM) Treatment

- High-dose steroid, e.g. Methylprednisolone 20-30mg/kg
- Oral steroid taper
- Plasma exchange in severe cases
- Full Recovery in 50-75%

Up to 50% develop multiple sclerosis - follow-up important
Other autoimmune encephalitis

- **Limbic encephalitis**: rare, paraneoplastic. Anti-Hu, GAD 65, Voltage-gated potassium channel, AMPA, GABA B
- **Rasmussen encephalitis**: unilateral, severe epilepsy
- **Hashimoto**: thyroid peroxidase antibodies
- **Opsoclonus-myoclonus syndrome**: associated with tumor (neuroblastoma) in 50%
5y old boy

- 2d history with balance problems, slurred speech, slow response, meaningless words
- respiratory tract infection for two weeks
- LP with 12 white cells, 11 lymphocytic
- virus and autoimmune screen normal
- MRI normal

Tentative diagnosis:

Mycoplasma pneumoniae associated encephalitis
Bacterial Encephalitis

- M. tuberculosis 5%-15%
- Listeria monocytogenes
- Mycoplasma pneumoniae 5-17%
- Spirochetes: Borrelia -Lyme disease, T. Pallidum
- Rickettsia: Q-fever, Rocky Mountain Spotted fever
- Ehrlichiosis
- Bartonella sp: Cat scratch disease
- Tropheryma whippelii: Whipple disease
Management

1. Rapid assessment and stabilisation

- ABC
- identify raised ICP
- treat fever/hypothermia
- treat seizures
- baseline samples: Full blood count, blood film, U&E, liver Function, glucose, CRP, sedimentation rate, ammonia, lactate, urine, Blood gas, blood culture, save frozen plasma and urine for later analysis
# Management

## 2. History, Examination and Evaluation

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Possible aetiological agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unvaccinated status</td>
<td>Polio, measles, mumps, rubella viruses</td>
</tr>
<tr>
<td>Animal contact</td>
<td>Rabies virus, cat scratch disease, Hendra virus, Q fever</td>
</tr>
<tr>
<td>Bird contact</td>
<td>WNV, Japanese encephalitis, <em>Cryptococcus neoformans</em></td>
</tr>
<tr>
<td>Insect contact</td>
<td>Malaria, WNV, tick-borne encephalitis virus, typhus, Lyme disease, trypanosomiasis</td>
</tr>
<tr>
<td>Ingested meat/unpasteurised milk</td>
<td>Toxoplasmosis, listeria, Q fever</td>
</tr>
<tr>
<td>Sexual contact</td>
<td>HIV, syphilis</td>
</tr>
<tr>
<td>Swimming</td>
<td>Enteroviruses, <em>Naegleria fowleri</em></td>
</tr>
<tr>
<td>Camping/hunting</td>
<td>Malaria, tick-borne encephalitis virus, typhus</td>
</tr>
</tbody>
</table>
Management

2. History, Examination and Evaluation

The Americas
- West Nile, La Crosse, St Louis, dengue, rabies

Europe/Middle East
- Tick-borne encephalitis, West Nile, rabies

Africa
- West Nile, Rift Valley fever virus, Crimean-Congo hemorrhagic fever, dengue, rabies

Asia
- Japanese encephalitis, West Nile, dengue, Murray valley encephalitis, rabies, Nipah

Australasia
- Murray valley encephalitis, Japanese encephalitis
Management

2. History, Examination and Evaluation

- General examination (rash? other organ involvement?)
- Neurological exam (focal deficit? brainstem symptoms?)
- Eyes (pupils? papiledema?)
Management

2. Investigations

Bloods and swabs

- Malaria
- Resp virus
- Mycoplasma
- etc.

Lumbar puncture

- cell count/differential, protein, glucose
- microscopy and culture
- PCR and antibodies for HSV1+2 and VZV (most important)
- PCR for enterovirus, HHV 6+7, CMV, EBV, respiratory viruses and as indicated in risk factors

HSV PCR sensitivity only 75% in children, 10% encephalitis have normal CSV -consider re-puncture!
2. Investigations

Lumbar puncture - contraindications

- a Glasgow coma score of less than or equal to 8
- a deteriorating Glasgow coma score
- focal neurological signs
- had a seizure lasting more than 10 minutes and has a GCS less than or equal to 12
- shock
- clinical evidence of systemic meningococcal disease
- papillary dilation (unilateral or bilateral)
- papillary reaction to light impaired or lost
- bradycardia (heart rate less than 60 beats per minute)
- hypertension (mean blood pressure above 95th centile for age)
- abnormal breathing pattern
- an abnormal doll’s eyes response (an abnormal response is random movement or no movement relative to the eye socket on turning the head to the left or right, or no upward gaze on flexing the neck)
- an abnormal posture
- signs of raised intracranial pressure

RCPCH  child with reduced consciousness guidelines
2. Investigations

Neuroimaging

CT

MRI
2. Investigations

EEG

- exclude subtle seizure or non-convulsive status epilepticus
- clues for specific diagnosis (e.g. PLEDs in HSV)
- confirm abnormal background activity
Management

3. Treatment

Aciclovir
- 500mg/m² x3 < 12y
- 10mg/kg x3 12-18y
- 20mg/kg x3 neonates

e.g. Ceftriaxone
- 80mg/kg x1

Additional treatment

Mycoplasma
Listeria
Rickettsia (tick-bite)
Toxoplasma gondii
CMV
Influenza
Measles
Bartonella Henselae

azithromycin
amoxicillin
fluoroquinolone (<8y), doxycycline
sulfadiazine+pyrimethamine
ganciclovir+foscarnet
oseltamivir
ribavirin
doxycycline+rifampicin
Outcome

DuBray et al, 2013: 190 children with encephalitis:
• 67% recovered, 33% incomplete recovery incl. 13 deaths
• risk factors: neuroimaging, GCS < 7, ethnicity
15y old boy

- HSV, VZV, EBV, CMV, entero- and parechovirus negative, normal autoimmune and paraneoplastic screen.
- MRI normal incl. vascular studies
- Treatment: Aciclovir stopped, Methylprednisolon bolus (15mg/kg) for 3 days, improved to near normal
- relapse 5 weeks, treated with methylpred. bolus and plasma exchange
- gradual improvement
- continued to have episodes of hypersomnia and personality change
Assumed diagnosis:

Autoimmune encephalitis with unknown antibody?

• 3rd lumbar puncture with WBC count 26/10⁹
• long term immunosuppression with low dose immunosuppression and mycophenolate mofetil
Right Diagnosis: Kleine-Levin Syndrome (episodic hypersomnia, mood changes, hypersexuality, hyperphagia)

- 3rd lumbar puncture with WBC count $27/10^9$
- long term immunosuppression with low dose immunosuppression and mycophenolate mofetil
Encephalitis - Definition

Inflammatory process of the brain with clinical evidence of neurological dysfunction

1. **Major Criterion**: Altered mental status (decreased level of consciousness, lethargy, personality changes) > 24h, no alternative explanation

2. **Minor Criteria**: Evidence of inflammation with:
   - fever within 72 hours before presentation
   - seizures
   - focal neurological deficit
   - inflammation on neuroimaging
   - CSF pleocytosis
   - EEG changes consistent with encephalitis

2 possible, 3 or more probable/confirmed

from: Vanketasan et al, 2013
Thank you for your attention!