The Clinical Epidemiology of Encephalitis

ESCMID Encephalitis Course
29-30 October 2014

Professor Tom Solomon
Director, Institute of Infection and Global Health, University of Liverpool
Director, NIHR Health Protection Research Unit in Emerging Infections
Chair of Neurology, Walton Centre NHS Foundation Trust
Head, Brain Infections Group
@RunningMadProf

- Introduction
  - Brain Infections Group, Institute of Infection & Global Health, Liverpool

- Epidemiology
  - Basic concepts and ideas
  - Changing epidemiology of encephalitis

- Some Examples
  - Europe
  - Global
  - Illustrative Cases
  - Our research, and others

Department of Epidemiology and Population Health
(Head: Matthew Baylis)
Department of Clinical Infection, Microbiology and Immunology
(Head: Nigel Cunliffe)
Department of Infection Biology
(Head: Jonathan Wastling)

Research themes:
- Understanding how pathogens cause disease – Lead: A. Kadioglu
- Improving the health of pets, working animals and their owners - Lead: A. Radford
- Tracking emerging and zoonotic infections – Lead: E. Fevre
- Enhancing food safety and food security – Lead: D. Williams
- Pioneering diagnostics, treatments and vaccines – Lead: N. French

Institute of Infection and Global Health
Director: Tom Solomon

NIHR Health Protection Research Unit in Emerging & Zoonotic Infections
Pathogen Detection & Characterisation
Clinical Surveillance
Epidemiological Approaches
Risk Assessment of Emerging & Zoonotic Threats
NIHR - £3.9M
The Brain Infections Group Research Disciplines

**Translation Research**
- Pathogenesis
  - Molecular Virology
  - Inflammation
  - Histopathology
  - Disease models

**Experimental Medicine**
- Clinical Research
  - Clinical Epidemiology
  - Pathophysiology
  - Case management
  - Treatment trials

**Public Health**
- With WHO
  - Disease burden
  - Education
  - Vaccine implementation

**Research Areas**
- HIV Brain Disease
- Enterovirus 71, Rabies
- Jap Enceph. Dengue, West Nile
- Dual CNS Infections
- Herpes encephalitis

**Liverpool Brain Infections Group International Collaborations**
- University of Oxford-Wellcome Trust Clinical Research Unit, Centre for Tropical Diseases, Ho Chi Minh City (since 1994)
- Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, Thailand (since 1994)
- Institute of Health and Community Medicine, Universiti Malaysia Sarawak, Malaysia (since 1997)
- University of Texas Medical Branch, Galveston, Texas (since 2001)
- Queen Elizabeth Hospital, Blantyre, Malawi (since 2003)
- National Institute for Mental Health and Neurological Science (NIMHANS), Bangalore, India (since 2004)
- Centers for Disease Control Atlanta, and Colorado, Texas (since 2007)
- Kanti Children’s Hospital, Kathmandu, Nepal (since 2009)
- Indian Institute for Science, Bangalore (2009)
- Johns Hopkins Baltimore, USA (2009)
- Washington University St Louis, USA (2009)
- Lerner Research Institute, Cleveland, Ohio (2010)
Epidemiology?

Epidemiology

- "the science that studies the patterns, causes, and effects of health and disease conditions in defined populations.
- It is the cornerstone of public health, and informs policy decisions and evidence-based practice by identifying risk factors for disease and targets for preventive healthcare."

Clinical epidemiology

- The application of the science of epidemiology in a clinical setting. Emphasis is on a medically defined population, as opposed to statistically formulated disease trends derived from examination of larger population categories.

Epidemiology

- Who gets disease?
- Any impact of Disease control?
  - Vaccination? Other?

- Clinical epidemiology
- In addition:
  - how do they present, clinical features?
  - Diagnostics important, treatment?

Life as a virus
Reproduction

10 genes
24,000 genes

Viruses

Hiders and Jumpers

Brain Infections:
- How does pathogen get into the body?
- How does it get into the Central Nervous System?
### Jumping Viruses

**Routes of spread?**
- Respiratory
- Gastrointestinal
- Mucosal
- Insect-borne
- Injections
- Congenital (mother to child)
- Sexually transmitted

---

**Respiratory**

---

**Gastrointestinal**


---

**Mucosal**


---

**Insect-borne**

[www.news.liv.ac.uk/](http://www.news.liv.ac.uk/)

---

**Sexually Transmitted**
Tropical Viral Infections

- Six questions to get a handle
  - What is the Natural host?
    - Animals (zoonoses)
    - Humans
    - Unknown
  - What is the habitat?
    - Urban
    - Rural
  - How is it transmitted?
    - Direct
    - Arthropod-borne (insects/ticks)
    - Both
  - Is there nosocomial spread?
  - Where?
    - On Globe
  - What disease syndrome?
    - Haemorrhagic (VHF)
    - FAR (fever arthralgia rash)
    - CNS
    - Other

Definitions

- Pathogen
  - Bacteria, virus, parasite, causing disease
- Zoonotic Infections
  - Spread from animals to humans
- Arbovirus infections
  - Arthropod-borne viruses,
    - i.e transmitted by insects or ticks (arthropods)

Zoonoses - Infections that spread from animals to humans account for majority of emerging infections

Emerging diseases – why?

- Increasing & more rapid human travel
- Overpopulation
- Changing agricultural
- Global warming
- Better diagnostics
- Better reporting
- Greater awareness

Airline Routes – No. Of airlines flying each route
Ebola risk: direct and indirect flights

USA at greatest risk of importing Ebola

Neuroanatomy

- Meningitis
  - Inflammation of meninges
  - Headache, vomiting, photophobia, neck stiffness, Kernig's signs. CSF pleocytosis

- Encephalitis
  - Viral invasion/inflammation of brain parenchyma
  - Behavioral change, 'psychiatric illness', confusion, coma, focal signs, convulsions

- Myelitis
  - Spinal cord (anterior horn cells)
  - Flaccid limb paralysis, absent reflexes

What are the key neuroscience questions?

- How does the pathogen get into the CNS?
- How does the pathogen damage neurones?
  - Can we do something to stop it?
- How much does the host response contribute damage?
  - Can we do something to stop it?

How does the pathogen get into the CNS?

Two paradigms

Tracking up a nerve
- Herpes simplex virus
- Rabies virus

Viraemia and spread across the BBB
- Japanese encephalitis virus
- Enterovirus 71
### Viral causes of encephalitis

<table>
<thead>
<tr>
<th>Group</th>
<th>Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes viruses</td>
<td>Herpes simplex virus type 1, Herpes simplex virus type 2, Varicella zoster virus type 1, Epstein-Barr virus, Cytomegalovirus, Human herpes virus 6 &amp; 7</td>
</tr>
<tr>
<td>Enteroviruses</td>
<td>Enterovirus 70, Enterovirus 71, Poliovirus, Coxackieviruses, Echoviruses, Parechovirus</td>
</tr>
<tr>
<td>Paramyxoviruses</td>
<td>Measles virus, Mumps virus, others (rarer causes)</td>
</tr>
<tr>
<td>Others (rarer causes)</td>
<td>Influenza viruses, Adenovirus, Parvovirus B19, Lymphocytic choreomeningitis virus, Rabies virus, others (rarer causes)</td>
</tr>
</tbody>
</table>

| Zoonotic viruses | Babesia, Borrelia, Ehrlichia, Bartonella Bartonella, P. falciparum, Lymphocytic choreomeningitis virus, Rabies virus, others (rarer causes) |

<table>
<thead>
<tr>
<th>Alphaherpesvirusae ancestors</th>
<th>Rhinovirus, coronavirus, paramyxovirus, coronavirus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus (family Picornaviridae)</td>
<td>Poliovirus, Coxackievirus, Echovirus, Parechovirus</td>
</tr>
<tr>
<td>Bovineparoviruses</td>
<td>Leishmania virus, Togavirus, other viruses</td>
</tr>
<tr>
<td>Caudovirales</td>
<td>Coxsackievirus, echovirus, parechovirus</td>
</tr>
</tbody>
</table>

### Epidemiology of encephalitis

- **Some pathogens** constant across globe, e.g., HSV
- **Others** varies with geography, e.g., Arthropod-borne & Zoonotic
- **HIV** and other immunocompromise has changed epidemiology
- **CMV, EBV, Toxoplasma** more important
- **Vaccination** has changed epidemiology in some places
  - Polio, Measles, Mumps, Japanese encephalitis

### Arboviruses — growing in importance

- West Nile virus in USA and Europe
- Tick-borne encephalitis virus in Europe
- Dengue and Chikungunya spreading

### Impact of
- climate change?
- Changing agricultural practice
- People movement
- etc

### Encephalitis Incidence

- 12,000 articles screened → 87 papers reviewed → 25 examined incidence of encephalitis

Jmor et al 2008
Incidence of Acute Encephalitis Syndrome (AES)
- Case definitions and diagnostic criteria, aetiologies, study types and reliability varied
- Incidence varies with geography, and age
- Western industrialised settings, incidences of AES
  - 10.5–13.8 per 100,000 for children
  - 2.2 per 100,000 for adults
- All age groups, incidences of AES
  - 6.34 per 100,000 tropical settings
  - 7.4 per 100,000 Western setting.

Mr KR, Hx, Exam
- 52 male, 1 week Hx of
- Fever, frontal headache, malaise, lethargic, Sleeping ++
  - 15 hrs/day
- Occ blurring of vision
- Poor coordination
- Hiccoughs 24hrs
- No photophobia, No neck stiffness
- Mild dry cough, watery diarrhoea, itching after hot bath
- 2/12 earlier Scuba Diving in Egypt
- PMHx Hep A 1996
- O/E
  - Pyrexial 38.5, NIL else
  - CXR normal
  - Na 127

Thoughts & next steps?
- CT
- Start antibiotics
- LP
- Observe
- Malaria film

Differential, Progress
- Day 1 DD ?SBE, infective, tropical, ?underlying malignancy
- Day 2, SHO
- DD ?Atypical pneumonia
  - (chest clear, sats 99%)
- BCs, malaria film, Rx clarithromycin
- Haloperidol for hiccoughs
- Day 3
- Temp Up, Periph WCC up
- Day 5
- Still headache, temp 40, voice sl slurred, v sleepy (haloperidol)
- CT head

What would you do next?
- CT
- Start antibiotics
- LP
- Observe
- Malaria film
Day 5, 19.00pm LP done
Day 6, 10.30am, results
  - WCC 220 (lymphocytes),
  - RCC<4, Protein 1.75, Gluc 2.5
Orientated in T, S & P
Await AFB, d/w neurosurgery
D7 Repeat bloods
D8, insuff CSF for TB/AFB
Neurologist called: Imp Meningitis / Encephalitis
Rx IV Aciclovir, await MRI brain
CSF positive by PCR for HSV type 1

The basics

- Encephalopathy – definition
  - Syndrome of Altered consciousness
  - Many cases included infections, metabolic, etc
- Encephalitis – definition
  - Strictly pathological diagnosis, inflammation brain parenchyma
  - Surrogate markers used
  - Causes
    - Viral, small intracellular bacteria, parasites immune mediated

Learning Points from this case

- Presentation can be subtle, fluctuant
- Clues
  - Lethargy Drowsiness, Sleeping 15hrs/day,
    Severe Headache, Hiccoughs, SIADH
  - Beware “atypical pneumonia”
- Chase and act on LP result

HSV encephalitis annual incidence

- Most studies 2-4 per million, annually
  - 1-2 per 250,000, annually
  - Each DGH (300,000) 2-3 cases per year
- USA (Johnstone 1998)
  - 2000 annually (population 291 million)
  - 6.9 per million annually
- UK Hospital Statistics (Davison et al EID 2003)
  - 120-175 cases annually (1989-98) (population 60 million)
  - 2-3 per million

Incidence – Any Viral Encephalitis

- Most studies: 5-10 per 100,000
  - Expect 3000-6000 annually in UK
- Average DGH (300,000)
  - 15-30 cases per year
  - 1-2 viral encephalitis per month
- UK Hospital Episode Statistics
  - 6400 cases of suspected encephalitis in 10 years
  - 1.5 per 100,000 (under-reporting)
  - 3800 unspecified
  - 1400 HSV
  - 300 VZV
  - 64 “exotic”
    - (measles mumps, rubella, adenovirus, LCMV)

HSV encephalitis

- Most is HSV type 1
  - Oral transmission
- About 10% HSV type 2
  - Genital transmission
  - (more often causes meningitis)
  - Causes encephalitis in immunocompromised adults, and neonates
  - In children → consider for sexual abuse
What are the clinical features of encephalitis?

- **Classically**
  - Flu-like prodrome, rapidly followed by severe headache, nausea, vomiting, altered consciousness, seizures, focal signs, meningism
- **Subtle presentations**
  - Low grade fever, behavioural changes, speech and language disturbances
  - Especially in immunocompromised

Why encephalitis is missed

- Wrongly attributing a patient’s **fever and confusion**
  - “urinary tract infection”
  - “chest infection”
- Failure to **recognise a febrile illness**.
  - “afebrile on admission”
- **Ignoring a relative** says patient behaviour, “not quite right”
  - “Glasgow coma score <15”
- Wrongly attributing clouding of consciousness
  - “drugs or alcohol”
- Failure to properly investigate a patient with a fever and seizure

- **Failure to do a lumbar puncture, even though there are no contraindications**

New UK guidelines on encephalitis

Management Algorithm

Understanding and Improving the Outcome in Encephalitis

National Institutes for Health Service Research (NIHR) Programme Grant
Common to both meningitis and encephalitis studies

ENCEPH-UK programme

Clinical predictors & clinical outcomes

Quality of Life & Health economics

End-user experience

Neuropsychological outcomes

Development of Randomised cluster trial

Aetiology & Disease mechanisms

UK-ChiMES (UK Childhood Meningitis & Encephalitis cohort Study)

Meningitis study

Intervention randomised cluster trial


Exotic

1% HSV

22% VZV

5% Adenoviruses

2% Other

60% Unknown

HDV 22%

Exotic 1%

V2V 0%

Adenoviruses 2%

Other 8%

From Davison et al. Emerg Infect Dis. 2003

Encephalitis in the UK

Alder Hey Children’s Hospital

Walton Centre for Neurology & Neurosurgery

Royal Liverpool University Hospital

University Hospital Aintree

Royal Preston Hospital

Hope Hospital

Manchester Royal Infirmary

Royal Manchester Children’s Hospital

Birch Hill Hospital, Rochdale

Fairfield General Hospital, Bury

North Manchester General Hospital

Rochdale Infirmary, Rochdale

The Royal Oldham Hospital, Oldham

Torbay District General Hospital

Royal Devon and Exeter Hospital

North Devon District Hospital, Barnstaple

Derriford Hospital

Barts & the London

Great Ormond Street

Guy's and St. Thomas’

King’s College Hospital

National Hospital for Neurology & Neurosurgery

Royal Free Hospital

St. George’s Hospital

University College Hospital

Chelsea & Westminster

Hammersmith Hospital

St. Mary’s Hospital

Causes of encephalitis & differences in their clinical presentations in England: a multicentre, population-based prospective study

Encephalitis Mimics

Granerod et al, Lancet ID 2010

Causes of encephalitis [No. (% 95%CI)]

Immunocompetent patients(n=172) Immunocompromised patients(n=31)

Hepatitis simplex virus 37 (21%, 16–28) 1 (3%, 0·1–17) 38

Acute disseminated encephalomyelitis 23 (14%, 9–19) .. 23

Antibody-associated encephalitis 15 (9%, 5–14) 1 (3%, 0·1–17) 16

Mycobacterium tuberculosis 9 (5%, 2–10) 1 (3%, 0·1–17) 10

Varicella zoster virus 4 (2%, 0·6–6) 6 (19%, 7–37) 10

Streptococci 4 (2%, 0·6–6) .. 4

Enterovirus 3 (2%, 0·4–5) .. 3

Dual finding 3 (10%, 2–26) 3

Epstein-Barr virus 1 (0%, 0–17) 1

HIV 1 (0%, 0–17) 1

JC virus 1 (0%, 0–17) 1

Lyme borreliosis 1 (0%, 0–17) 1

Pneumococcus 1 (0%, 0–17) 1

Other 13 (8%, 4–13) .. 13

Unknown 64 (37%, 30–45) 11 (35%, 19–55) 75

Granerod et al, Lancet ID 2010
**What are the clinical features of encephalitis?**

### Clinical features [No. (%), 95%CI] of encephalitis in HPA study

<table>
<thead>
<tr>
<th>Feature</th>
<th>All encephalitis* (n=203)</th>
<th>HSV (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>147 (72, 66–78)</td>
<td>29 (76, 60–89)</td>
</tr>
<tr>
<td>Headache</td>
<td>122 (60, 53–67)</td>
<td>16 (42, 26–59)</td>
</tr>
<tr>
<td>Seizures</td>
<td>105 (52, 46–59)</td>
<td>24 (63, 46–78)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>111 (55, 48–62)</td>
<td>16 (42, 26–59)</td>
</tr>
<tr>
<td>Irritability</td>
<td>75 (37, 30–44)</td>
<td>11 (29, 15–46)</td>
</tr>
<tr>
<td>Personality/behavioural change</td>
<td>131 (64, 57–71)</td>
<td>24 (63, 46–78)</td>
</tr>
<tr>
<td>Stiff neck</td>
<td>46 (23, 17–29)</td>
<td>5 (13, 4–28)</td>
</tr>
<tr>
<td>Focal neurology</td>
<td>73 (36, 29–43)</td>
<td>16 (42, 26–59)</td>
</tr>
<tr>
<td>Coma (GCS&lt;/=3)</td>
<td>37 (18, 13–24)</td>
<td>9 (24, 11–40)</td>
</tr>
<tr>
<td>Neurological signs**</td>
<td>61 (30, 24–37)</td>
<td>9 (24, 11–40)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms††</td>
<td>98 (48, 41–55)</td>
<td>13 (34, 20–51)</td>
</tr>
<tr>
<td>Respiratory symptoms††</td>
<td>41 (20, 15–26)</td>
<td>5 (13, 4–28)</td>
</tr>
<tr>
<td>Rash**</td>
<td>23 (11, 7–16)</td>
<td>2 (5, 0–6–18)</td>
</tr>
<tr>
<td>Photophobia**</td>
<td>16 (8, 5–12)</td>
<td>3 (6, 2–21)</td>
</tr>
<tr>
<td>Urinary symptoms††</td>
<td>21 (10, 6–15)</td>
<td>1 (3, 0–1–14)</td>
</tr>
</tbody>
</table>

*Granerod et al, Lancet ID 2010*

---

**Varicella encephalitis**

- Rare
- Vasculitis involved in pathology
- No evidence but treatment usually with aciclovir & steroids
- Varicella may also cause other neurological presentations including para/post infectious cerebellitis, myelitis, stroke

---

**Neurologic Complications of the Reactivation of Varicella-Zoster Virus**

![Diagram showing the progression of neurologic complications](image)

*Gilden et al NEJM 2000*
History

• Linh, 4-year-old in Southern Vietnam
• Four-day illness.
• 2 days High fever, runny nose, cough, and sore throat.
• No vomiting or diarrhoea.
• Day 3 mother bought a mixture of unknown drugs at a local store - did not lower the fever.
• Day 4 Confused, her eyes rolled up, and she had intermittent twitching and spasms in her face.

Examination

• Temperature was 39°C, pulse 132, respiratory rate 40, blood pressure 110/80.
• No rash or lymphadenopathy;
• heart sounds were normal;
• Bilateral coarse crackles in the chest
• Abdominal examination was normal.
• **Neuro Exam** - Signs?
  • Unconscious
  • - an abnormal flexion response to pain,
  • - no eye movements,
  • - no verbal response to pain.
  • Continuous twitching - left side of face.
  • No neck stiffness.
  • Limbs were flaccid with absent deep tendon reflexes in the legs.

Differential diagnosis

• Arboviral encephalomyelitis
• Japanese encephalitis, other
• Other viral encephalitis
• Herpes Simplex Virus 1, Herpes Zoster Virus, Enterovirus
• Polio, Rabies
• Acute Disseminated encephalomyelitis
• Post infectious – measles
• Post vaccine
• Bacterial Meningitis/Abcess
• TBM
• Cerebral Malaria
• Tetanus
• Drugs/Toxins
• Secondary Bacterial Pneumonia

Qn 2 List the investigations you would do?
CNS (central nervous system) Infections in Asia
- What are the causes?
- Can we improve diagnosis?
- Can we improve outcome?

Japanese encephalitis virus (JEV)
- Flavivirus, Flaviviridae
- West Nile virus
- Dengue

Envelope (E) protein important in viral entry into cells
4 genotypes of JEV recognised

Japanese encephalitis (JE)
- 70,000 cases/year
- 10-30% mortality
- Vaccines
  - Expensive
  - Not available to most
- No antiviral treatment

Thirty-two areas endemic for JE in 24 Asian and Western Pacific countries sorted into 10 incidence groups
- Approx 57 900 JE cases typically occur annually
  - 1.8 per 100 000
  - 5.4 per 100 000 in children

Estimated global incidence of Japanese encephalitis: a systematic review

CNS Study: diagnoses in 378 patients
Japanese encephalitis: Epidemiology

- Cycle
  - Birds -> pigs -> humans
- Vector
  - Culex tritaeniorhynchus
- Rural/Peri-urban
- Virus ubiquitous
- 1 in 300 infections symptomatic
- SE Asia, India, Western Pacific, China
  - Summer epidemics in temperate North
  - Endemic/sporadic in tropical South
- Expanding
  - 40-60,000 cases/year
  - children/adults in Asia
- Non immune adults susceptible

Diagnosis

Diagnostic arbovirology

- Detection of NS1 antigen

Clinical Features

- Fever, headache, coma
- Convulsions*
  - ?subtle motor Sz
- Raised ICP*
- Polio-like flaccid paralysis
- Parkinsonism
  - mask-like facies
  - cogwheel rigidity
  - tremor
- Outcome
  - 20% fatal,
  - 40% sequelae
  - 30% recovery
- Complications *
  - pneumonia
  - malnutrition
  - contractures
  - bedsores

* Management

Clinical features represent the anatomical location (Parkinsonism, flaccid paralysis); seizures and raised intracranial pressure may be treatable
Disease Control

Vaccines against JE

The Liverpool Outcome Score
a simple tool for assessing outcome in Japanese encephalitis

Road Blocks to Vaccine Implementation

Disease Burden
- Death
- Disability
- Health economics

Surveillance
- Recognition
- Diagnosis

Vaccination
- Demand

Japanese Encephalitis Control Partners

Bill & Melinda Gates Foundation
GAVI
National and State Ministries of Health of 26 countries
AFRIMS
World Health Organization
unicef
International Pediatric Association

19 million children immunized in India in 2006
Japanese encephalitis Control Programme: 2005-2013

- Vaccination in 11 new countries
- More than 200 million vaccinated
- Estimated 854,000 cases and 214,000 deaths avoided
- Associated saving US$ 1.024 billion across Asia

Japanese encephalitis is spreading – why?

Climate Change and Japanese encephalitis

Japanese encephalitis cases – 2004

Japanese encephalitis cases – 2005

Japanese encephalitis cases – 2006
Japanese encephalitis cases – 2007

Maximum Parsimony Phylogeny of the Flaviviruses

- Cell Fusing Agent
- Apo
- Rio Bravo
- Powassan
- Langat
- Louping Il
- Tick Borne Encephalitis
- Yellow Fever
- Dengue - 4
- Dengue - 2
- Dengue - 3
- Dengue - 1
- St Louis encephalitis
- West Nile
- Kunjin
- Murray Valley Encephalitis
- Japanese Encephalitis

West Nile virus arrives in USA

Welcome to Texas
Age-specific incidence and seroprevalence of Japanese Encephalitis in endemic areas of Asia and West Nile encephalitis in nonendemic areas of Europe.

JEV serogroup ancestor

MVE

1,3

1,2,3

1,2

1,2,3
Spread of recent JEV genotypes?

Transmission of Japanese encephalitis virus through mosquito vectors

Dengue
- Mosquito-borne flavivirus
  - Dengue Fever / DHF
  - 100 million cases per year

NEurological Manifestations of Dengue
- 5% of suspected CNS infections
  - 6 (4.2%) of 378 CNS patients vs. 4 (1.4%) of 286 controls [OR 3.1 (1.7-5.8 p=0.039)]

- Pathophysiology
  - Encephalopathy as part of severe DHF
  - Dengue viruses cross blood brain barrier
    -> 'encephalitis'

Similar incidence reported in Thailand, India [Chokephaibulkit, K. Pned ID 2002]
Model of flavivirus neurotropism
CHIKV in plasma samples of 8 (14%) of 58 children with suspected central nervous system infection in Bellary, India.

CHIKV was also detected in the cerebrospinal fluid of 3 children.

**Rabies** is under-recognised and under-reported. Rabies encephalitis is common in Malawi and can be misdiagnosed as cerebral malaria. - *Emerging Infectious Diseases* 2007, 13: 136-9

**Diagnostics of CNS Infections**

- Rabies is under-recognised and under-reported.
- Rabies encephalitis is common in Malawi and can be misdiagnosed as cerebral malaria. - *Emerging Infectious Diseases* 2007, 13: 136-9

**Viral Central Nervous System Infections in Children from a Malaria-Endemic Area of Malawi: a Prospective Cohort Study**

- 513 children with suspected CNS infection
  - Excluded bacterial
  - 94 (18%) died.
- 163 (32%) had P. falciparum parasitaemia, of whom 34 died;
- 133 (26%) had at least one virus detected in the central nervous system (CNS) by polymerase chain reaction (PCR), with 43 deaths.
- Twelve different viruses were detected,
  - adenovirus most common (42 patients).
- 45 (9%) children had both parasitaemia and viral infection;
  - 27 (54%) of 78 diagnosed clinically with cerebral malaria.

**Aedes albopictus in Europe 2008 and predicted impact of climate change**

**DIAGNOSTICS OF CNS INFECTIONS**

- Rabies is under-recognised and under-reported.
- Rabies encephalitis is common in Malawi and can be misdiagnosed as cerebral malaria. - *Emerging Infectious Diseases* 2007, 13: 136-9

**Viral Central Nervous System Infections in Children from a Malaria-Endemic Area of Malawi: a Prospective Cohort Study**

- 513 children with suspected CNS infection
  - Excluded bacterial
  - 94 (18%) died.
- 163 (32%) had P. falciparum parasitaemia, of whom 34 died;
- 133 (26%) had at least one virus detected in the central nervous system (CNS) by polymerase chain reaction (PCR), with 43 deaths.
- Twelve different viruses were detected,
  - adenovirus most common (42 patients).
- 45 (9%) children had both parasitaemia and viral infection;
  - 27 (54%) of 78 diagnosed clinically with cerebral malaria.
Another Case

Human Enterovirus 71 (HEV71)

- Family Picornaviridae, Genus Enterovirus
  - Genogroups A, B(1-4), C(1-4)
  - Human Enterovirus Species A

- Isolated in 1969 California
  - Stool of a child with viral encephalitis
  - Faeco-oral spread
- 1970s-80s Sporadic cases / modest outbreaks (all continents)
  - 1975 Bulgaria
  - 1978 Hungary

- Clinically
  - Hand foot and mouth disease (HFMD)
  - Neurological disease (aseptic meningitis, encephalitis, paralysis)
  - Pulmonary oedema
Brainstem encephalitis in EV71

T2 weighted MRI, mid-sagittal


EV71 outbreaks across Asia

- 1997
  - Sarawak
- 1998
  - Peninsular Malaysia, Singapore, Japan, Taiwan (Est 1.5 million cases - Huang, NEJM, 1999)
  - Perth
- 2000
  - Sarawak, Singapore, Korea, Japan, Taiwan, Sydney
- 2001
  - Taiwan, Sydney

Emergence of new subgenotypes during outbreaks

- 68 Genogroup B4
- 68 Genogroup C1
- 41 Genogroup B5 (newly emerged)

Genogroups of HEV-71 differ in their virulence


Funding

wellcome trust
PATH
BILL & MELINDA GATES FOUNDATION
National Institute for Health Research
The Leverhulme Trust

Medical Research Council
Liverpool Neurological Infectious Diseases Course
Liverpool Medical Institution

Feedback from previous course:
- "Would unreservedly recommend to others"
- "An excellent 2 days! The best course for a long time"
Convenors: Prof Tom Solomon, Deitan Carroll, Rachel Kneen & Dr Nick Beeching
www.liv.ac.uk/neuroidcourse email braininfections@liv.ac.uk

@RunningMadProf
- YouTube Channel: Tom Solomon
  - "Sex Drugs & Emerging Viruses"
  - Does Liverpool Have the World’s Biggest Brain?

@RunningMadProf Facebook.com/RunningMadProf