ENCEPHALITIS

CLINICAL APPROACH OF UNCOMMON, EMERGING AND TRAVELING CAUSES OF ENCEPHALITIS

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ETIOLOGY CLEAR?
CALIFORNIA ENCEPHALITIS PROJECT

• 1998-2000 No underlying cause identified in 62% (208 /334)
  – ~10% of patients ultimately received a diagnosis of a noninfectious condition.
• In a follow-up report of 1570 cases over a 7-year period
  – Confirmed or probable etiologic: 16%
  – Possible etiology identified: 13%
    • Viral: 69%
    • Bacterial 20%
    • Prion 7% -- Parasitic 3% -- Fungal 1%


CLINICAL CASE 1

• Woman, 25 year
• No medical history
• Recent travel to South Africa, Costa Rica and Peru
• 2015: admitted for obturation, headache, fever, impression of petechiae, clinical exam neck stiffness
• Management on admission: Ceftriaxone
## LAB RESULTS

### SEROLOGIE

<table>
<thead>
<tr>
<th>VIRUSSEN</th>
</tr>
</thead>
</table>
| Dengue IgG (ELISA) | 0.77 Negatief  
| Dengue IgM (ELISA) | ↑ 6.73 Positief  
| West Nile IgG (ELISA) | ↑ 2.47 Positief  
| West Nile IgM (ELISA) | 0.04 Negatief  
| Tick-Borne Encephalitis IgG (IFAT) | Negatief  
| Tick-Borne Encephalitis IgM (IFAT) | Negatief  

### BACTERIËN

|  
|----|
| **Rickettsia conorii** (IgG) | Negatief  
| **Rickettsia typhi** (IgG) | Negatief  
| **Leptospirose (MAT)**  
| Grippotyphosa Duyster | Negatief  
| Javanica poi | Negatief  
| Canicola canicola | Negatief  
| Hebdomadis hebdomadis | Negatief  
| Ballum ballum | Negatief  
| Pomona proechimys | Negatief  
| Ict.icterohaemorragiae | Negatief  
| Ict. copenhageni | Negatief  
| Sejroe hardjo | ↑ 1/6400 Negatief  
| Semaranga patoc | ↑ 1/800 Negatief  
| Leptosp. sneltest IgM | Zwak positief  

LEPTOSPIROSIS

• A case-control study in Taiwan
  - Hemorrhagic diathesis (odds ratio [OR] 10; 95% CI 1.1-90.8)
  - Myalgias (OR 8.0; 95% CI 1.4-45.8)
  - Bilateral enlarged kidneys (OR 7.5; 95% CI 2.5-22.7)
  - Sterile pyuria (OR 6.3; 95% CI 1.4-27.8)
  - Hypokalemia (OR 5.0; 95% CI 1.1-22.3)
  - Thrombocytopenia (OR 4.8; 95% CI 1.1-21.1)

• Complications
  - Jaundice and renal failure ("Weil's disease")
  - Pulmonary hemorrhage & acute respiratory distress syndrome (ARDS),
  - Myocarditis,
  - Rhabdomyolysis
  - Uveitis

LEPTOSPIROSI

• Aseptic meningitis is observed in 50 to 85 percent after seven days of illness.
  – Attributed to a host immune response to the organism rather than to direct infection.

• 90 percent of serologically confirmed cases of leptospirosis with CSF abnormalities had Leptospira DNA detectable in the CSF by polymerase chain reaction


WEST NILE VIRUS

- Arthropod-borne virus, Culex
- Most human infections are asymptomatic.
- Clinical symptoms occur in ≈20% of case-patients
- Fever, headache, and myalgia; <1% of WNV infections develop into severe neuroinvasive disease

- Clinical diagnosis may be difficult because WNV infections resemble other (arbo)viral diseases.

- Laboratory
  - Serologic testing.
  - Reverse transcription PCR (RT-PCR) can be used to detect viral RNA during the acute phase of the disease (but only low level viremia and short lived)

WEST NILE VIRUS IN A BELGIAN TRAVELER

- A 73-year-old Belgian woman, who had a medical history of lymphoma, traveled to Kavala city (Macedonia, Greece)
- Developed 6-day history of fever, headache, malaise, nausea, confusion, decline of consciousness, and neck stiffness

<table>
<thead>
<tr>
<th>Sample</th>
<th>Date</th>
<th>RT-PCR (Ct value)</th>
<th>WNV ELISA IgM (ratio)</th>
<th>WNV ELISA IgG (ratio)</th>
<th>Flavi IFAT IgM</th>
<th>Flavi IFAT IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>Aug 15</td>
<td>Positive (45.47)</td>
<td>Positive (25)</td>
<td>Negative</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>CSF</td>
<td>Sep 3</td>
<td>ND</td>
<td>Positive (5.16)</td>
<td>Positive (2.21)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Serum</td>
<td>Sep 6</td>
<td>Positive (42.87)†</td>
<td>Positive (4.76)</td>
<td>Positive (2.63)</td>
<td>WNV positive</td>
<td>WNV positive§</td>
</tr>
</tbody>
</table>

*WNV, West Nile virus; RT-PCR, reverse transcription PCR; Ct, cycle threshold; Flavi, flavivirus; IFAT, indirect fluorescent antibody technique; ND, not done; CSF, cerebrospinal fluid.
†The ELISA is positive if ratio >1.1 for IgM and >1.5 for IgG. The cutoff value for IFAT is 1/10 for both IgG and IgM.
§Sequencing revealed a 116-bp sequence perfectly matched to the WNV amplicon and is highly suggestive for WNV lineage 2 on the basis of the presence of 2 specific nucleotides.

Strongest signal for WNV, weak signal for other flaviviruses (Japanese encephalitis virus, dengue viruses 1–4, yellow fever virus).

CLINICAL CASE 2

- Man, 38 years, No medical history
- Travel to Austria mid February 2015
- On day of return: confused, confabulation, aggressive, disoriented, complains of headache
- Day after return: admitted to hospital in comatose condition
- Management: Ceftriaxone high dose, Acyclovir
- All microbiological assays negative, including TBE
- No signs of temporal encephalitis
- EEG showed no sign of lateralization
- Lumbar puncture: High white blood cell, lymphocytic formula, high protein
How important is FSME in Belgium?

- Not at all - No urgency with end user (traveller) - campers, youth movement
- Not endemic
- Hardly imported (or detected)
  - 2012: Two cases imported
    - 1 Austria & 1 Norway
    - The attack rate: 0.5-1.3 per 100 000 (1 per 77 000-200 000) overall in Western/Central Europe endemic areas for the exposed at-risk population.

CLINICAL CASE 3

• 31-year-old man
• morbilliform rash, pharyngitis, and a fever (40ºC) and diarrhoea.
• Neurological examination on admission was normal.
• However, 3 days later, he became lethargic and had a tonic-clonic seizure, necessitating intubation and mechanical ventilation.
• HIV screening tests done on admission were positive, indicating seroconversion.


Figure: MRI of the brain (diffusion-weighted image)
The cortex of the brain is diffusely hyperintense, a reflection of the severe disturbance of the diffusion of the protons in the cells, due to cytotoxic oedema.
CLINICAL CASE 3

• Culture of blood and cerebrospinal fluid, serology, and PCR did not demonstrate active infection with
  – herpes simplex virus
  – varicella zoster virus
  – Epstein-Barr virus
  – Cytomegalovirus
  – JC virus
  – Borrelia burgdorferi, Treponema pallidum, mycobacteria, other bacterial pathogens, fungi, or toxoplasma.

CLINICAL CASE 4

- 05/2015 Headache & fever
  - Augmentin
- Yellow fever vaccination (23/04)
- Travel through Toscany (tree plantations)
- Medical History: neuritis optica

- MRI: The radiologist saw two small lesions occipital

- CSF:
  - Erythrocytes 0/µl   0-5
  - Leucocyte 52/µl
    - Lymfocyten: 86 %
  - Glucose 60 mg/dl  40-70
  - Lactate 2.6 mg/dl  10.0-22.0
  - Totaal eiwit 70 mg/dl  15-40
  - Oligoclonal production IgG
    - (type IV Immunoreaction)
# CLINICAL CASE 4

<table>
<thead>
<tr>
<th>ID</th>
<th>COLLECTED</th>
<th>TYPE</th>
<th>5´-NC assay(^1)</th>
<th>Panflavivirus assay(^2)</th>
<th>Panarenavirus assay(^3)</th>
<th>IgM IIF</th>
<th>IIF IgG</th>
<th>YF PRNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>09042</td>
<td>11.05.2015</td>
<td>Serum</td>
<td>NEG</td>
<td>NEG</td>
<td>NEG</td>
<td>ND!</td>
<td>ND!</td>
<td>ND!</td>
</tr>
<tr>
<td>09542</td>
<td>12.05.2015</td>
<td>RNA</td>
<td>NEG</td>
<td>NEG</td>
<td>NEG</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>09542</td>
<td>12.05.2015</td>
<td>CSF</td>
<td>EQUIVOCAL</td>
<td>NEG</td>
<td>NEG</td>
<td>NEG</td>
<td>NEG</td>
<td>ND</td>
</tr>
<tr>
<td>12868</td>
<td>16.05.2015</td>
<td>Serum</td>
<td>NEG</td>
<td>NEG</td>
<td>NEG</td>
<td>1:20</td>
<td>1:800</td>
<td>1:106</td>
</tr>
<tr>
<td>20141</td>
<td>26.05.2015</td>
<td>CSF</td>
<td>EQUIVOCAL</td>
<td>NEG</td>
<td>NEG</td>
<td>NEG</td>
<td>1:400</td>
<td>1:16</td>
</tr>
</tbody>
</table>
Figure 1. General safety profile of the licensed YF vaccine, Stamaril®, in terms of most frequently reported AEs during the period 1 January 1993 to 27 September 2010. Events are listed by MedDRA System Organ Class and Preferred Term for each System Organ Class that includes at least 5% of reported AEs. Top panel presents number of events reported, regardless of age, bottom panel presents number of events reported for adults older than 60. AEs: Adverse events; SAEs: Serious adverse events YF: Yellow fever.
CLINICAL CASE 4

- Mycob. tuberculosis PCR Negatief
- West Nile IgG (ELISA) Negatief
- West Nile IgM ELISA) Negatief
- West Nilevirus PCR Negatief
- Gele koorts IgG Negatief
- Gele koorts IgM Positief < 1:100
- Gele koorts IgM * Positief < 1:10
- Tick-Borne Enceph. IgG Negatief
- Tick Borne Enceph. IgM Negatief
- Sandfly fever IgG Negatief
- Sandfly fever IgM Negatief
- (*) Onduidelijke interpretatie. Graag opvolgstaal aub
SANDFLY FEVER – PAPATACCI VIRUS

Figure 1
Distribution of (a) Toscana, (b) Sicilian, and (c) Naples viruses in the European Union and neighbouring countries around the Mediterranean Sea up to 2009

Countries with confirmed cases are depicted in mid grey, the estimated distribution limits are depicted with a dark grey line. Source: V-borne project; reproduced with permission from the European Centre for Disease Prevention and Control.

TOSCANA VIRUS: SEVERE PRESENTATIONS

- Bunya viridae
- Pappataci fever
- Surveillance for mild non neurologic febrile illness
- 7 cases/358 screened
- 4/7 Mild aseptic meningitis
- 3/7 atypical presentation
  - 2/3: persistent infection
    - Meningoencephalitis
    - Ischemic complications
  - 1/3: febrile exanthema
CLINICAL CASE 5

- 10-year-old Belgian girl who stayed
- July 2004 in Shanghai as expatriate
- Mid-July 2004: flu-like syndrome developed into encephalitis; no specific diagnosis
- Serology
  - Herpes (IgG and IgM) and for JE (IgM) were negative in Shanghai
- Mid-August 2004: dramatically worse, repatriated
- Serology for Herpes varicella/zoster en Herpes simplex (IgG) positive - (resp. 3880 en 4193) - PCR LCR negative - no data on IgM serology.

- Presumptive treatment for Herpes encephalitis

- Serology for JE when in Belgium:
  - 24 Aug 2004: IgG = 32 - IgM = 256;
  - 2 Oct 2004 IgG = 256 and IgM = 32
  - Serologic tests showed declining IgM and increasing IgG titers = recent seroconversion for JE
JE is the leading cause of viral neurological disease and disability in Asia\(^1,2\)

- 35,000 – 50,000 cases of symptomatic JE are reported among residents of Asia each year\(^3\)
- Cases are reported primarily in children\(^4\)
- Children under 15 years of age are at most risk of JE in countries without childhood immunization programs\(^4\)
  - Immunologically naïve adults (e.g. travelers) have the same risk of infection as children living in endemic areas\(^4\)
- Reporting of JE is inexact. In some locations, under-reporting may occur due to lack of surveillance and laboratory diagnostic capacity\(^5\)

\(^3\) Solomon T et al. Lancet 2003; 361: 821-826
\(^6\) Centers for Disease Control and Protection. Travelers’ Health: Yellow Book. Chapter 2. 2010
DIAGNOSIS OF JE CAN BE CHALLENGING\(^1\)

- Patients who fall ill after JE infection generally do so after an incubation period of 5 to 15 days\(^2\)

**Symptoms of JE include:**

| At an early stage:  | • Headache  
|                    | • Fever (39 – 40°C)  
|                    | • Nausea and vomiting  
|                    | • Gastrointestinal disorders (in children)\(^2,3\)  
| Could Progress to: | • Focal neurological deficits  
|                    | • Changes in mental status or behavior  
|                    | • Generalized weakness and movement disorders\(^2,3\)  

- Diagnosis of JE can be extremely challenging as the clinical features are indistinguishable from other types of encephalitis\(^1\)
- Laboratory tests are required to analyze the patient’s cerebrospinal fluid and blood for viral antibodies which provide a specific diagnosis\(^1\)

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\(^2\) Centers for Disease Control and Prevention. Travelers’ Health: Yellow Book. Chapter 2. 2010

\(^3\) Oya A & Kurane I. J Travel Med 2007; 14: 259-268
CLINICAL CASE 6

- Two medical students were hospitalized in Chicago with a 10-day history of progressively worsening headache, neck pain, and paresthesia.
- Part of a group of 23 travelers to Jamaica
- CSF consistent with the presence of aseptic meningitis; one patient had 36 percent eosinophils.
- Over the next week and a half, seven fellow travelers from two states were hospitalized with meningitis.

Angiostrongylus cantonensis

New England Journal of Medicine, 346(9), 668–675. 
http://doi.org/10.1056/NEJMoA012462
FAST GROWING AFRICAN LAND SNAIL

And is is used in the food industry as…

French Style Giant African Land Snail
<table>
<thead>
<tr>
<th>Priority area</th>
<th>Research needed</th>
</tr>
</thead>
</table>
| Diagnosis                         | • Rapid, accurate, low-cost, point-of-care diagnostic tests for infections that affect the nervous system  
• Clinical diagnostic algorithms for infections that affect the nervous system  
• Improved testing for detection of infection-related nervous-system disabilities                                                                 |
| Epidemiology                      | • Accurate incidence and prevalence estimates of common infections that affect the nervous system  
• Accurate identification and frequency estimates of nervous-system manifestations and sequelae  
• Identification of potentially modifiable risk factors specific to infections that affect the nervous system |
| Pathogenesis                      | • Identification of host response pathways that lead to nervous-system deficits or to clinical immunity  
• Identification of pathogen factors that lead to nervous-system deficits or to clinical immunity  
• Assessment of risks and interactions of co-infections and co-morbidity                                                                 |
| Vaccine development               | • Develop safe and effective vaccines based on immunology, epidemiology and pathogenesis studies  
• Phase I and II trials  
• Phase III trials                                                                                                                                   |
| Treatment                         | • Effective adjunctive treatment to prevent or decrease nervous-system deficits or disabilities  
• Low cost, low toxicity antimicrobials that work against drug-resistant pathogens  
• Multi-site, large clinical trials that provide definitive answers on interventions  
• Effective or improved primary treatment of infection                                                                                             |
| Rehabilitation                    | • Effective and feasible physical, occupational and cognitive rehabilitation programmes                                                                 |
| Operations and implementation     | • Optimal methods to implement or operationalize interventions with known efficacy                                                                 |

**Globally Research Priorities for Infections That Affect the Nervous System**

1. The diagnostic approach must include neuroimaging—either MRI or CT. If not used, document specific reasons.

2. Empirical antimicrobial therapy should include rapid administration of intravenous acyclovir at appropriate dosages; if appropriate, treatment for bacterial meningitis (ceftriaxone) and rickettsial or ehrlichial infection should be included.

3. Once an etiologic agent of encephalitis is identified, antimicrobial therapy should be targeted, or therapy should be discontinued if treatment is not available.

KEEP LAUGHING IN THE FACE OF DIAGNOSTIC AND THERAPEUTIC ADVERSITY!

Dirk Ommeslag ®
ACKNOWLEDGEMENTS

And don’t forget Oropouche virus!!

http://www.promedmail.org/post/4224847