SEIZURES AND COMA IN A TRAVELLER RETURNING FROM THE TROPICS

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No conflicts of interest relating to this presentation
CASE PRESENTATION

- Male 28 years old, without significant medical history
- Spent 8 days in Malaysia with his girlfriend (including a 2 day trip in Malaysian Borneo district for rafting)
- Residence in 5 star hotel, no consumption of non-commercial food or drinks
- No contact with animals or insect bites
- Malaria prophylaxis with atovaquone proguanil and good anti-mosquito protective measures
- Pre-travel consultation: had previous effective vaccination against hepatitis B and A
- He had a superficial abrasion in his left foot during outdoor activities without evidence of infection
CASE PRESENTATION

- Day 3 of his return: mild symptoms of illness, fever 38.0°C, sore throat, headache
  - Treated with paracetamol, symptoms disappeared after 48 hours of bed rest

- On day 14, he develops new fever up to 39°C, malaise, myalgias, retroorbital headache, vomiting, diarrhea and mild erythematous rash of the trunk
  - His girlfriend found him unconscious at home
  - On the way to the hospital he developed seizures
CASE PRESENTATION

- Glasgow coma scale 5
- Meningism
- Dyspnoea, tachypnea (RR 32/min), Hypoxia (SaO2 90%, FiO2 0.6)
- Bilateral Ronchi, Xray: bilateral alveolar –interstitial infiltrates, peripherally
- Oliguria, metabolic acidosis pH 7.29; base excess, – 6.1 mmol/L
- Electrocardiogram (ECG): sinus tachycardia (110bpm) with inferolateral T wave inversion
- Arterial blood pressure 90/55 mmHg
CASE PRESENTATION
LAB TESTS AT HOSPITAL ADMISSION

- HT 30%
- HB 9.2mg/dL
- PLT 70 000/mm³
- WBC 13 000/mm³ (Poly 48%, Lympho 40%, Eo 0.2%)
- Urea 120mg/dL
- Creatinine 4.8 mg/dL
- Gluc 95mg/dL
- ALT 1228 IU/L
- AST 2301 IU/L
- ALP 430 IU/L
- Gt 65 IU/L
- Tbil 14.1 mg/dL
- Dbil 10.9 mg/dL
- Urinalysis: granular casts, WBCs, protein ++
Q1: WHICH IS THE MOST PROBABLE DIAGNOSIS?

1. Malaria
2. Viral Encephalitis/meningitis
3. Typhoid fever
4. Rickettsial infection
5. Eosinophilic meningitis
6. All the above
7. Other
# Relative Risks for Travellers

<table>
<thead>
<tr>
<th>Risk</th>
<th>Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Acute viral gastroenteritis, <em>E. coli</em> enteritis, upper respiratory infection</td>
</tr>
<tr>
<td>Moderate</td>
<td>Salmonella, shigella, campylobacter, giardia, hepatitis A, gonorrhoea, chlamydia, herpes simplex, dengue, Epstein-Barr, malaria (without chemoprophylaxis)</td>
</tr>
<tr>
<td>Low</td>
<td>Malaria (with chemoprophylaxis), amoebiasis, leptospirosis, typhoid, cholera, HIV, HBV, syphilis, chancroid, Lyme, schistosomiasis, tuberculosis, ascariasis, enterobiasis, strongyloidiasis, trichuriasis, rubella, rubeola, rickettsioses, borreliosis, tropical sprue</td>
</tr>
<tr>
<td>Very low</td>
<td>Yellow fever, rabies, anthrax, plague, trypanosomiasis, viral haemorrhagic fevers, filariasis, flukes, toxocariasis, diphtheria, legionella, tularemia, melioidosis, poliomyelitis, echinococcosis, trichinosis, gnathostomiasis, anisakiasis, yaws, pinta, LGV</td>
</tr>
</tbody>
</table>
Q2: WHAT FURTHER TESTS WOULD YOU ASK?

1. Brain MRI
2. Malaria testing
3. Serology for WNV, CHIKGV, Dengue, arboviruses, rickettsiae, leptospira and tuberculosis testing
4. All the above
5. Other
CASE 2
ON ADMISSION

Radiology
- U/S abdomen: mild hepatomegaly and splenomegaly
- Brain C/T: non significant

Lumbar puncture
- Lymphocytic pleocytosis (385 cells/mm³, lymphocytes 90%)
- Gluc: within normal range
- Protein slightly elevated
- Gram stain and latex negative
- PCR for bacterial pathogens: negative
CASE PRESENTATION

- Over the next 2 days, his condition deteriorated
  - High fevers, tachycardia (heart rate, 120/min), hypotensive (BP 80/64 mmHg), hypoxia (PO$_2$, 71.9 mmHg; FIO$_2$, 0.6), jaundice (bilirubin, 18.5 mg/dL), progressive renal failure (creatinine, 6.1 mg/dL)

- On day three in the ICU
  - The white cell count was 16400/mm$^3$ and the platelet count dropped to 10000/mm$^3$
  - He became anuric (renal replacement treatment started), developed new seizures and ARDS
  - He developed rhabdomyolysis with creatinine phosphokinase (8037 IU/L [RR, 0–250 U/L])
MANAGEMENT

- Intubation/mechanical ventilation
- Fluids+inotropes, PLT-blood transfusions
- Artesunate+doxycycline iv
- Ceftriaxone
- Serial malaria smears
ED EVALUATION OF THE FEBRILE TRAVELER

1. What infections are possible given the patient’s travel history
2. What infections are probable given the patient’s medical history and presentation
3. What infections are life-threatening or contagious or both
PRACTICAL APPROACH TO AN III TRAVELER WITH SEIZURES AND COMA

Diagnosis

- Basic blood work (CBC, BMP, LFT, urinalysis, blood cultures)
- Thick and thin blood film
- Imaging studies (CT, MRI)
- Lumbar puncture
- Special tests (EEG)
- Serology and viral identification

BMP indicates basic metabolic panel; CBC, complete blood picture; EEG, electroencephalogram; LFT, liver function test

Han M, Neurologist. 2005 January; 11(1): 30–44
LABORATORY RESULTS

- Thick and thin blood films examined twice for malaria parasites were negative
- Blood cultures were negative
- Targeted testing was negative for:
  - Dengue fever, CHIKG (serology)
  - WNV (serology and PCR in blood and CSF)
  - Rickettsia (serology), Leptospiras (serology)
  - Influenza viruses A and B (antigen, serology)
  - Adenovirus, Enteroviruses (PCR)
  - Toxoplasma (serology)
  - Legionella (urine antigen, serology)
  - Cytomegalovirus (serology, PCR), Epstein–Barr virus (serology)
  - HIV (ELISA, PCR)
Q3: WHAT ARE YOUR THOUGHTS NOW?

1. Malaria
2. Viral Encephalitis
3. Rickettsial infection
4. Leptospirosis
5. All the above are still possible
6. Other
Malaria

Areas with malaria: Present in rural areas of Malaysian Borneo (Sabah and Sarawak Provinces) and to a lesser extent in rural areas of Peninsular Malaysia.

Estimated relative risk of malaria for US travelers: Low.

Drug resistance: Chloroquine.

Malaria species: *P. falciparum* 40%; *P. vivax* 50%; remainder *P. Knowlesi, P. malariae, and P. ovale*. *P. knowlesi* reported to cause 28% of cases in Sarawak and known to cause cases in both Malaysian Borneo and Peninsular Malaysia.

Recommended chemoprophylaxis: Atovaquone-proguanil, doxycycline, or mefloquine.

Yellow Fever (√) (not required)

Requirements: Required if traveling from a country with risk of YFV transmission and ≥1 year of age, including transit >12 hours in an airport located in a country with risk of YFV transmission

Other Vaccines to Consider

Routine, hepatitis A & B, *typhoid*, Japanese encephalitis, and rabies

PRACTICAL APPROACH TO AN ILL TRAVELER

Travel history: date and places visited
Fever: duration, pattern
Potential exposures:
  - Travel to rural areas
  - Sexual exposure
  - Freshwater swimming
  - Climatic conditions, season (rainy)
  - Ingestion of contaminated food
  - Insect or animal bites
  - Exposure to ill people or injuries
Vaccination history
Use of prophylactic medication and compliance
Use of protective equipment
Immune status

Biphasic?
## INCUBATION PERIODS
### PATHOGENS CAUSING CNS INVOLVEMENT IN THE RETURNED TRAVELLER

<table>
<thead>
<tr>
<th>Short (&lt;10 days)</th>
<th>Medium (11-21 days)</th>
<th>Long (&gt;30 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Viral haemorrhagic fevers</td>
<td>- Malaria (particularly <em>P. falciparum</em>)</td>
<td>- Malaria</td>
</tr>
<tr>
<td>- Dengue Fever</td>
<td>- Typhoid fever</td>
<td>- Viral hepatitis</td>
</tr>
<tr>
<td>- Yellow Fever</td>
<td>- Leptospirosis</td>
<td>- Schistosomiasis</td>
</tr>
<tr>
<td>- Arboviral infections</td>
<td>- Rickettsioses: scrub typhus, spotted fever group, Q fever</td>
<td>- Tuberculosis</td>
</tr>
<tr>
<td>- Enteric bacterial infections (including paratyphoid)</td>
<td>- Brucellosis</td>
<td>- Amoebic liver abscess</td>
</tr>
<tr>
<td>- Enteric viral infections</td>
<td>- Enteric protozoal infections</td>
<td>- Enteric protozoal infections</td>
</tr>
<tr>
<td>- <em>Rickettsioses</em>: louse, flea-borne, typhus</td>
<td>- Enteric hepatitis</td>
<td>- Enteric helminthic infections</td>
</tr>
<tr>
<td>- Pneumonia, Influenza</td>
<td>- Strongyloides</td>
<td>- HIV</td>
</tr>
<tr>
<td>- Anthrax</td>
<td>- Lyme</td>
<td>- Rabies</td>
</tr>
<tr>
<td>- Bacterial meningitis</td>
<td>- African trypanosomiasis</td>
<td>- Leishmaniasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- American trypanosomiasis</td>
</tr>
</tbody>
</table>
PRACTICAL APPROACH TO AN ILL TRAVELER WITH SEIZURES AND COMA

Management

Treat potential life-threatening complications
Assess for neurologic emergencies (status epilepticus, stroke, spinal cord compression)
Consider empiric broad-spectrum antibiotic, antiviral or antiparasitic coverage for very ill patients
Consult tropical or travel medicine expert
CNS INVOLVEMENT AND FEVER AND THROMBOCYTOPENIA/PETECHIAES

- Severe malaria
- Coma, lethargy, delirium, seizures, retinal haemorrhages
- Dengue Haemorrhagic Fever
- Leptospirosis, Rickettsial infections
- Mental Status changes, seizures
- Meningococcaemia,
- Yellow fever, viral haemorrhagic fevers,

Spira AM, Lancet. 2003;361(9367):1459-69
### Differential Diagnosis of Physical Findings for Some Travel Diseases

<table>
<thead>
<tr>
<th>Condition</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy</td>
<td>Plague, HIV, rickettsioses, brucellosis, leishmaniasis, dengue, lymphogranuloma venereum, Lassa fever</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Malaria, leishmaniasis, amoebic liver abscess, typhoid, hepatitis, leptospirosis</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Malaria, leishmaniasis, trypanosomiasis, typhoid, brucellosis, typhus, dengue</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Hepatitis, malaria, leptospirosis, relapsing fevers, cholelithiasis, pancreatitis</td>
</tr>
<tr>
<td>Petechiae/ecchymosis</td>
<td>Meningococcaemia, yellow fever, dengue, rickettsioses, viral haemorrhagic fevers, envenoming, leptospirosis</td>
</tr>
<tr>
<td>Nystagmus/diplopia</td>
<td>Rabies, botulinum poisoning, neurotoxic snakebite envenoming</td>
</tr>
</tbody>
</table>

Adapted from Spira A, Lancet 2003; 361: 1459–69
Q4: IS DIAGNOSIS OF MALARIA EXCLUDED SO FAR?

1. Yes
2. No
Q5: IS DIAGNOSIS OF LEPTOSPIROSIS EXCLUDED SO FAR?

1. Yes
2. No
PITFALLS

- Malaria (serial smears, requires lab experience, rapid diagnostic methods, PCR, *P. knowlesi* infection difficult to diagnose)
- Leptospirosis (no optimal testing method)
  - Phase-specific diagnostic methods, early diagnosis difficult
- Rickettsia (fatal if not treated early, difficult to diagnose early)
- Biphasic fever
- Dengue and leptospirosis

Spira AM, Lancet. 2003;361(9367):1459-69
CASE PRESENTATION

- The patient succumbed on the 10\textsuperscript{th} ICU day due to multiorgan failure
- Brain haemorrhage was demonstrated on MRI
- Broad spectrum antibiotics had been added to cover nosocomial sepsis
- Fever never responded to treatment
Q6: WHICH TEST LED TO THE DIAGNOSIS?

1. PCR and/or rapid test for malaria
2. Dark field urine microscopy and repeat serology/PCR for *Leptospira spp*
3. Repeat serology for Dengue fever
4. Other
Q7: WHICH IS THE MOST PROBABLE DIAGNOSIS?

1. Malaria
2. Dengue haemorrhagic fever
3. Leptospirosis
4. Other
PCR in the urine was positive for *Leptospira interrogans*
LEPTOSPIROSIS

- A zoonosis of worldwide distribution (World Health Organization, 1999), caused by infection with pathogenic spirochaetes of the genus *Leptospira*.

- The disease is maintained in nature by chronic renal infection of carrier mammals, which excrete the organism in their urine.

- It has been recognized as an emerging infectious disease, in part because of recent large-scale outbreaks associated with recreational activities.

THE CAUSATIVE BACTERIUM

Order Spirochaetales – Treponema, Borrelia, Leptospira

Family – Leptospiraceae

Genus – Leptospira, 26 serogroups, 250 serovars

interrogans, biflex, icterohemorrhagica

Long, Thin, Highly Coiled

Dark Field Microscopy
LEPTOSPIROSIS

- First description by Weil in 1886. Synonyms: Rice fever, mud fever, canicola fever, leptospira jaundice, etc.
- Humans become infected through direct exposure to infected animals or their urine, or through indirect contact via contaminated water or soil, or inhalation of droplets infected from animal urine.
RISK GROUPS

Rural > Urban
Male > Female (10 : 1)

Occupational exposure
- Farmers – Rice, Sugarcane, Vegetables
- Sewerage workers; Abattoirs, Butchers
- Veterinarians, Lab staff, Miners, Soldiers
- Fishermen – Inland (not on the sea)

Recreational activities
- Swimming, Sailing, Marathon runners, Gardening
CLINICAL PRESENTATION

- **Anicteric**
  - Common, mild
  - < 2% Mortality

- **Icteric**
  - Rare, Severe
  - 15-40% Mortality

90% of Cases

10% of Cases
<table>
<thead>
<tr>
<th></th>
<th>Anicteric leptospirosis</th>
<th>Icteric leptospirosis (Weil’s syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fever</strong></td>
<td>First stage 3-7 days (Septicemic)</td>
<td>First stage 3-7 days (Septicemic)</td>
</tr>
<tr>
<td></td>
<td>Second stage 0 days-1 month (Immune)</td>
<td>Second stage 10-30 days (Immune)</td>
</tr>
<tr>
<td><strong>Important clinical findings</strong></td>
<td>Myalgia, headache, abdominal pain, vomiting, conjunctival suffusion, fever</td>
<td>Meningitis, uveitis rash, fever</td>
</tr>
<tr>
<td></td>
<td>Jaundice, hemorrhage, renal failure myocarditis</td>
<td></td>
</tr>
<tr>
<td><strong>Leptospires present</strong></td>
<td>Blood</td>
<td>Blood</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>CSF</td>
</tr>
<tr>
<td></td>
<td>Urine</td>
<td>Urine</td>
</tr>
</tbody>
</table>
ICTERIC LEPTOSPIROSI

LIVER
Jaundice, occurs in 4-6 days
Serum bilirubin markedly increased (20-40 mg/dl)
AST/ALT mild elevations
Hepatocellular necrosis/intrahepatic steatosis

KIDNEYS – Mild to Severe
Urinalysis: Hematuria / Pyuria / Proteinuria
Renal Failure: Pre renal azotemia, Oliguric / Non Oliguric
HEMORRHAGIC MANIFESTATIONS

Hemorrhagic Fever - Vascular injury
    Respiratory, Gastrointestinal, Renal & Genital tracts

Hemorrhagic Pneumonitis
    Hemoptysis / Respiratory failure
    Occurs in 2nd week (as early as 24-48 hours)
CARDIAC INVOLVEMENT

**Cardiac manifestations**
- Hemorrhagic Myocarditis
- Cardiomyopathy / Cardiac failure
- Arrhythmias, Hypotension / Death
- Atrial fibrillation / Conduction defects

**ECG changes**
- Non Specific ST-T changes
- Low voltage complexes
CNS AND OCULAR INVOLVEMENT

Aseptic Meningo-encephalitis

It is rare; It occurs in the Immune phase

CSF – proteins ↑, lymphocytes ↑

Convulsions, Encephalitis, Myelitis & Polyneuropathy

Ocular manifestations

Late complication; Conjunctival suffusion/hemorrhage

Anterior uveitis, Iritis, Iridocyclitis, chorioretinitis

Occurs in 2 weeks to 1 yr. (average 6 months)
LABORATORY TESTS FOR DIAGNOSIS OF LEPTOSPIROSIS

- Early diagnosis difficult: Culture for Leptospira (delays), PCR variable, genus specific
- IgM ELISA / (M)SAT: Microscopic Slide Agglutination Test (>5 day)
- Diagnosis of leptospirosis is usually accomplished retrospectively by serology
- Microscopic agglutination test (MAT); Sero conversion or 4 fold rise/ high titer

MAT

1 week 1 month 2 months 1 year 5 years

ELISA or SAT

Levett, 2003
**WHO GUIDE - FAINÉ’S CRITERIA**

<table>
<thead>
<tr>
<th>Score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Headache</td>
</tr>
<tr>
<td>2</td>
<td>Fever</td>
</tr>
<tr>
<td>2</td>
<td>Temp &gt; 39 F</td>
</tr>
<tr>
<td>4</td>
<td>Conj. suffusion</td>
</tr>
<tr>
<td>4</td>
<td>Meningism</td>
</tr>
<tr>
<td>4</td>
<td>Muscle pain</td>
</tr>
<tr>
<td>1</td>
<td>Jaundice</td>
</tr>
<tr>
<td>1</td>
<td>Alb, ↑ creatinine</td>
</tr>
<tr>
<td>5</td>
<td>Rain fall</td>
</tr>
<tr>
<td>4</td>
<td>Contaminate H₂O</td>
</tr>
<tr>
<td>1</td>
<td>Animal contact</td>
</tr>
<tr>
<td>15</td>
<td>ELISA IgM + ve</td>
</tr>
<tr>
<td>15</td>
<td>SAT positive</td>
</tr>
<tr>
<td>15</td>
<td>MAT high titer</td>
</tr>
<tr>
<td>25</td>
<td>MAT rising titer</td>
</tr>
<tr>
<td>Definite</td>
<td>Culture positive</td>
</tr>
</tbody>
</table>

Score of 25 or more – Presumptive Diagnosis  
Score of 20 to 25 – Possible case of leptospirosis
TREATMENT

Mild-start Rx. early

- Oral Treatment 7 to 10 day
  - Doxycycline 100 mg b.i.d
  - Amoxicillin 500 mg q.i.d
  - Ampicillin 500 mg q.i.d

Severe-start intensive Rx.

- IV Treatment 5 to 7 days
  - Benzyl Penicillin 20L q.i.d
  - Ampicillin 1G q.i.d
  - 3rd gen Ceftriaxone 1G od/
    Cefotaxime 1G t.i.d

Jarisch Herxheimer Reaction
TAKE HOME MESSAGE FOR THE RETURNING TRAVELER:
FEBRILE PATIENT WITH CNS INVOLVEMENT

Except from “classic” CNS infections (viral/bacterial meningitis, encephalitis, protozoan infections of the brain), physicians should exclude:

- MALARIA
- Dengue (can be fatal, particularly in repeat infections /DHF)
- Rickettsia/Leptospira
  - Can be fatal if not treated early
  - Difficult to diagnose

Spira AM, Lancet. 2003;361(9367):1459-69
THANK YOU