Diversity of Central Nerve System Infection

Dr. Koon-Ho Chan
Dr. Yuan Gao, Dr. Ian Yu-Hin Leung

Division of Neurology
Department of Medicine
Queen Mary Hospital
The University of Hong Kong

May 14th 2019
Patient 1: F/21 student, good past health

- smoker (10 cigarettes/day), social drinker
- C/C : fever X 5 days
- HPI: fever (38-39.6%), myalgia over neck & back
diffuse headache, dizziness
no photophobia
- abdominal pain & vomiting for 5 d (clear fluid)
- no diarrhea, no intake of unclean or raw food
- no cough/sputum/SOB/RN/sore throat; no dysuria or hematuria
- no contact of febrile subjects, no recent travel outside HK
- swimming in waterfall river, hiking in Tai Po ~1 wk ago
- consulted GP, NPA (-ve), oral cefuroxime taken for 1 d, no improvement
Patient 1: Physical Examination

- alert, GC satisfactory, febrile 38.4°C, coherent speech
- mild neck stiffness
- Kernig’s sign -ve
- no rash
- no pallor, jaundice, cyanosis or ankle edema
- no palpable cervical or supraclavicular LN
- tenderness over neck and back muscles
- respiratory & cardiovascular systems: NAD
- abdomen: mild epigastric discomfort, no guarding or rebound
Patient 1: Investigations

- WCC 7.3 (N6.0, L0.91, monocyte 0.31), Hb 14.0, plt 82
- ESR 76 mm/hr, CRP 18.3 mg/dL
- Ur/Cr: 10.2/119, LFT normal, LDH 164
- clotting normal
- CXR clear
- blood C/ST -ve, NPA influenza virus A & B -ve
- serum IgM & IgG for Mycoplasma pneumonia, Coxiella burnetti, Borrelia burgdorferi, Dengue -ve
- Weil Felix test: NAD
- serum CMVpp65 Ag -ve
Patient 1

- CT brain: NAD; LP : OP 15 cm H2O
- CSF TCC 40 (L46%), prot 0.50 g/L, glu 2.6 mmol/L (5.0), Gram’s stain -ve
- Rx: IVF (1.5 L/d), empirically IV rocephin, ampicillin, & acyclovir
- CSF C/ST -ve, IgM for JEV & VZV -ve
- CSF PCR for HSV, VZV, enterovirus, MTB -ve
- fever subsided since D3, working Dx: viral meningitis
- microbiologist D3: suggested to stop rocephin & ampicillin
- MRI brain: NAD
Patient 1

- D6 deranged LFT: AST 91, ALT 100, bilirubin & ALP normal
- HBsAg, anti-HCV -ve
- microbiologist: acyclovir induced LFT derangement possible but unlikely, continue acyclovir
- AST, ALT improved spontaneously in following d
- generalized discomfort & mild headache persisted

Review:
1. Hx: open water swimming in waterfall river (Tai Po)
2. renal impairment on presentation
3. LFT derangement
Patient 1

- check leptospiral **serology**
- leptospiral IgM 17 U/ml (<15), IgG 5.5 U/ml (<5.0)
- doxycycline initiated, for 1 wk
- remained afebrile, headache subsided & GC improved
- paired sera confirmed *Leptospira Icterohaemorrhagiae* (MAT)
- FU 2 wk later: well
- repeat CBP, LRFT normal
- refused repeat LP
Leptospirosis

- caused by spirochetes of genus Leptospira
- of pathogenic species, over 250 serovars (by serotyping)
Leptospirosis

- transmission via broken skin, mucus membranes, conjunctiva
- contact with potentially infected animals, soil or surface water contaminated by animal urine
- workers in sewers, water sports e.g. canoeing
- direct oral intake of contaminated water or food: can also → infection
- rats & small rodents: main reservoir of infection for human
- human to human spread rarely, sexual transmission & via breast milk reported
<table>
<thead>
<tr>
<th>Occupation involving direct animal contact</th>
<th>Occupation involving indirect animal contact</th>
<th>Leisure activities involving indirect animal contact</th>
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<tbody>
<tr>
<td>Abattoir worker</td>
<td>Sewer worker</td>
<td>Open water swimming</td>
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<tr>
<td>Farmer/dairy farmer</td>
<td>Miner</td>
<td>Canoeing/Kayaking</td>
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<tr>
<td>Veterinary surgeon</td>
<td>Military personnel</td>
<td>Sailing/wind surfing</td>
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<td>Meat inspector</td>
<td>Septic tank cleaner</td>
<td>Potholing/caving</td>
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<tr>
<td>Rodent control worker</td>
<td>Fish farm worker</td>
<td>Adventure traveller</td>
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<tr>
<td>Pet shop owner</td>
<td>Canal and river worker</td>
<td>Fresh water fishing</td>
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<tr>
<td>Butcher</td>
<td>Watercress farmer</td>
<td>White water rafting</td>
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<tr>
<td>Animal shelter worker</td>
<td>Flood relief worker</td>
<td>Rowing</td>
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<td>Pet owner</td>
<td>Gravel pit worker</td>
<td>Orienteering/triathlon</td>
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<td>Gamekeeper</td>
<td>Street dweller/urban slums</td>
<td>Golf (stagnant pool traps)</td>
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<td>Construction and demolition site worker</td>
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<td></td>
<td>Plumber</td>
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<tr>
<td>Year</td>
<td>France</td>
<td>Malaysia</td>
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<tr>
<td>2006</td>
<td>France</td>
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<td>2007</td>
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<td>Borneo</td>
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<td>2008</td>
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<td>Cambodia</td>
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<td>2009</td>
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<tr>
<td>2010</td>
<td>Thailand</td>
<td>Cambodia</td>
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</tbody>
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Numbers in square brackets indicate the total number for each year. Several cases had visited more than one country and had several types of exposure.
# Leptospirosis

<table>
<thead>
<tr>
<th>Approximate time scale:</th>
<th>Week 1</th>
<th>2</th>
<th>3</th>
<th>4 (months-years)</th>
<th>years</th>
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<tbody>
<tr>
<td>Incubation period</td>
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<td>Inoculation</td>
<td>2 - 20 days</td>
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<td>Leptospires present in:</td>
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<td>Antibody Titres</td>
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<td>&quot;negative&quot;</td>
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<td>CSF</td>
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<td>Culture</td>
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<td>Serology</td>
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<tr>
<td>Phases</td>
<td>leptospiraemia</td>
<td>leptospiuria and immunity</td>
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</tbody>
</table>

- **Acute stage**
- **Convalescent stage**
- **Uveitis? interstitial nephritis**
- **Convalescent shedder**
- **Reservoir host**
- **Normal response**
- **Early treatment**
- **Delayed**
- **Titres decline at varying rates**
- **Anamnestic**

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**Legend:**
- **1:** Leptospiraemia
- **2:** Leptospiuria and immunity
- **3:** Convalescence
- **4:** Months-years
- **5:** Years
Leptospirosis: C/F

- mild leptospirosis: most common (~90%), majority mild anicteric febrile illness (similar to influenza)

- severe end: renal failure, liver failure & pulmonary haemorrhage

- presentations protean, most prominent at outset: headache, fever & myalgia

- myalgia with ↑ serum CK (often calf, also affect paraspinal & abdominal muscles) & conjunctival suffusion help to distinguish from other febrile illnesses

- liver: may have high bilirubin but relatively low ALP & ALT
1. Mild Leptospirosis
   Mild disease often self limiting or may represent "Phase 1" of more serious disease

2. Severe Leptospirosis
   "Weils disease"

- Pulmonary haemorrhage
- Renal failure, liver failure
- Rhabdomyolysis

- Jaundice, hepatomegaly
- Generalised vasculitis
- Meningoencephalitis

- Fever, myalgia (especially of calves), arthralgia
- Anorexia, nausea and vomiting
- Conjunctival suffusion, headache

Asymptomatic infection

Asymptomatic carriage or excretion of leptospires

DIAGNOSED AS LEPTOSPIROSIS

NOT DIAGNOSED AS LEPTOSPIROSIS
Leptospirosis: C/F

- **pulmonary**: small nodular densities, ground glass appearance, consolidation; pulmonary haemorrhage

- **haematological**: pancytopenia, TTP & DIC in severe cases

- **neurological**: meningitis or encephalitis, radiculopathies, transverse myelitis, CN palsies & GBS
Leptospirosis: C/F

- **cardiac**: myocarditis, pericarditis, conduction disturbance frequent (usu 1st degree AVB), widespread T-wave inv, AF & other arrhythmia, coronary arteritis, aortitis

- **renal**: interstitial nephritis, rhabdomyolysis (myositis in severe cases)

- **Risk factors for severe leptospirosis:**
  1. <5 & >65 yr
  2. serious health condition e.g. pneumonia
  3. immunocompromised status
  4. previously deranged liver f(x) e.g. alcoholic liver disease
Clinical description:
The usual presentation is an acute febrile illness with headache, myalgia (particularly calf muscle) and prostration associated with any of the following symptoms/signs:
- Conjunctival suffusion
- Anuria or oliguria
- Jaundice
- Cough, hemoptysis and breathlessness
- Hemorrhages (from the intestines; lung bleeding is notorious in some areas)
- Meningeal irritation
- Cardiac arrhythmia or failure
- Skin rash

Laboratory criteria
Presumptive diagnosis:
- A positive result of a rapid screening test such as IgM ELISA, latex agglutination test, lateral flow, dipstick etc.

Confirmatory diagnosis:
- Isolation from blood or other clinical materials through culture of pathogenic leptospirae.
- A positive PCR result using a validated method (primarily for blood and serum in the early stages of infection).
- Fourfold or greater rise in titer or seroconversion in microscopic agglutination test (MAT) on paired samples obtained at least 2 weeks apart. A battery of Leptospira reference strains representative of local strains to be used as antigens in MAT.
Leptospirosis: Dx

- Culture - difficult, time consuming
- PCR-based tests available, limited sensitivity: wide diversity of leptospira species & lack of standardization among assays
- Screening by ELISA for leptospira-specific antibodies
  - high IgM titre in single sample or 4-fold rise: recent infection
  - false negative in first wk, weak reactions may suggest very early/late phase, or non-specific
- Confirmatory Microscopic Agglutination Test (MAT)
  - Serogroup-specific test, positive if >= 1 in 320
  - serum reacted with suspensions of live leptospires
  - tightly agglutinated clumps of leptospires seen in +ve sera
  - end point: highest dilution of serum with 50% agglutination
  - agglutinating antibodies: IgM/IgG, detectable from D7-10
Leptospirosis: Diagnosis can be difficult

Actionable Diagnosis of Neuroleptospirosis by Next-Generation Sequencing

Michael R. Wilson, M.D., Samia N. Naccache, Ph.D., Erik Samayoa, B.S., C.L.S.,
Mark Biagian, M.D., Hiba Bashir, M.D., Guixia Yu, B.S.,
Shahriar M. Salamat, M.D., Ph.D., Sneha Somasekar, B.S., Scott Federman, B.A.,
Steve Miller, M.D., Ph.D., Robert Sokolic, M.D., Elizabeth Garabedian, R.N., M.S.L.S.,
Fabio Candotti, M.D., Rebecca H. Buckley, M.D., Kurt D. Reed, M.D.,
Teresa L. Meyer, R.N., M.S., Christine M. Seroogy, M.D., Renee Galloway, M.P.H.,
Sheryl L. Henderson, M.D., Ph.D., James E. Gern, M.D., Joseph L. DeRisi, Ph.D.,
and Charles Y. Chiu, M.D., Ph.D.

SUMMARY

A 14-year-old boy with severe combined immunodeficiency presented three times to a medical facility over a period of 4 months with fever and headache that progressed to hydrocephalus and status epilepticus necessitating a medically induced coma. Diagnostic workup including brain biopsy was unrevealing. Unbiased next-generation sequencing of the cerebrospinal fluid identified 475 of 3,063,784 sequence reads (0.016%) corresponding to leptospira infection. Clinical assays for leptoepirosis were negative. Targeted antimicrobial agents were administered, and the patient was discharged home 32 days later with a status close to his premorbid condition. Polymerase-chain-reaction (PCR) and serologic testing at the Centers for Disease Control and Prevention (CDC) subsequently confirmed evidence of Leptospira santarosai infection.

Leptospirosis and Weil’s disease in the UK

A.E. FORBES¹, W.J. ZOCHOWSKI², S.W. DUBREY¹ and V. SIVAPRAKASAM²
From the ¹Department of Cardiology, Hillingdon Hospital, Field Heath Road, Uxbridge, Middlesex,
UB8 3NN and ²Leptospira Reference Unit (LRU), Department of Microbiology, County Hospital,
Hereford, HR1 2ER, UK


The recent high-profile death of a British Olympic rower from leptoepirosis, acquired in the UK, has raised awareness among the public and the medical profession to this uncommon but potentially fatal disease. The re-emergence of the disease abroad is well documented in the literature,¹ but less is known about the cases in the UK. The increase in participation in water sports, foreign travel and often a combination of the two, has increased the exposure of tourists subsequently returning to the UK, from areas of high prevalence. The widespread nature of this disease is reflected by the variety of colloquial names by which it is known (Table 1). Leptospirosis is a zoonotic infection. The bacteria are shed in the urine of animals to the environment from where
Leptospirosis: treatment

- Rx for severe disease controversial as acute infections are self resolving

- WHO: Rx with antibiotics likely effective if initiated w/i 5 d of start of illness

- Some studies: IV antibiotics beneficial even given late in disease course for severe & advanced leptospirosis
Leptospirosis: treatment

- Cochrane review: advocate use of penicillin & doxycycline (insufficient evidence for clear guidelines)
- Disease duration shortened with antibiotics started within first 4 d of illness
- Mild disease: doxycycline 100mg BD x 1wk (or azithromycin 500mg daily x 3d for pregnancy)
- Severe disease: Pen G 1.5 MU Q6H or cephalosporins (ceftriaxone or cefotaxime) for 1wk
- Commencement of antibiotic Rx: may be a/w Jarisch-Herxheimer reaction (start within 1-2 h of Rx: fever, tachycardia, rigors & hypotension)
Leptospirosis: treatment

- Supportive Rx:
  1. dialysis: renal failure
  2. AED: seizures
  3. ICU care: status epilepticus

- severe leptospirosis has immune-mediated pathogenesis, methylprednisolone tried

- steroid use remain controversial (Forbes et al., 2012)

- IVMP 1 g daily X 3 d followed by oral prednisolone 1mg/kg X 7 d, benefit if given within 12 h of onset of pulmonary manifestation (Sheno et al., 2006)
Leptospirosis: prognosis

- worldwide: MR upto 22%, higher with poor health facilities
- fulminant Weil’s disease $\rightarrow$ cardiovascular collapse, pulmonary haemorrhagic pneumonitis, MR $\sim$50%

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Deaths in England and Wales attributed to Weil’s disease 2006–10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Occupation</td>
</tr>
<tr>
<td>Male</td>
<td>Unemployed</td>
</tr>
<tr>
<td>Male</td>
<td>Retired</td>
</tr>
<tr>
<td>Male</td>
<td>Guest House owner</td>
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<tr>
<td>Male</td>
<td>Catering manager</td>
</tr>
<tr>
<td>Male</td>
<td>Unknown</td>
</tr>
<tr>
<td>Male</td>
<td>Rowing instructor</td>
</tr>
</tbody>
</table>

$^a$Leptospires identified from blood culture identified as L. interrogans serogroup Icterohaemorrhagiae. Ictero: Icterohaemorrhagiae; HF: hepatic failure; J: jaundice; ND: serogroup not determined; Pul Haem: pulmonary haemorrhage; RF: renal failure; Resp Fail: respiratory failure.
Neuroleptospirosis - revisited: experience from a tertiary care neurological centre from south India


- out of 31 pts, 25 had LP done
- mean CSF TCC 50.2 ± 72 cells/μl (1-350); 7 of 25 pt (28%) normal CSF TCC (<5 cells/μl)
- lymphocytic pleocytosis in 13 of 18 pt (72%); neutrophil predominant in remaining pt
- CSF prot elevated in 22 pt (88%), normal in 3; mean CSF prot 1.15 ± 0.67 g/L (0.05-3.23)
- 6 (24%) had CSF sugar <60%, only one sugar <40%

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients survived (group A: n=23)</th>
<th>Patients expired (group B: n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF protein (mg %)</td>
<td>90.6 ± 45.7</td>
<td>183.3 ± 73.2*</td>
</tr>
<tr>
<td>Deep coma (%)</td>
<td>8.7</td>
<td>25**</td>
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*P< 0.001 compared to group A (t test)
**P< 0.037 compared to group B (Fisher’s exact test)
Case 2

- 49/M, Chinese, GPH, no statin exposure
- PHx: **Anti-SRP Ab associated IMNM** diagnosed in 06/2018
- Subacute proximal limb weakness and mild dysphagia
- HyperCKemia 17,304 IU/L
- EMG: irritable myopathy
- Muscle biopsy: necrotizing myopathy
- Anti-SRP Ab (+), anti-Ro52 Ab (+), anti-HMGCR Ab (-)
- PET-CT: no malignancy, pneumonitis changes (+)
- Prednisolone and azathioprine since 07/2018
Case 2

- **C/C:** acute onset dysarthria 11/2018 (prednisolone 25 mg daily & azathioprine 125 mg daily)
- no fever/rash, mild coughing, no neck pain, no headache
- preceding bilateral LL numbness & buttock pain for weeks
- **P/E**
- General: no rash, no meningism
- Neurology: no cortical signs, dysarthria (+), symmetrical bilateral UL/LL proximal limb weakness 4/5, neck flexion 4/5, sensation intact, reflexes preserved, plantar downgoing
Figure 1. Acute ischemic infarct of bilateral basal ganglia: NECT brain reveals bilateral basal ganglia hypodensity; MRI DWI and ADC sequences demonstrate bilateral basal ganglion diffusion restriction suggesting acute infarct with post-contrast enhancement of left basal ganglia lesion.
Figure 1. Acute ischemic infarct of bilateral basal ganglia: NECT brain reveals bilateral basal ganglia hypodensity; MRI DWI and ADC sequences demonstrate bilateral basal ganglion diffusion restriction suggesting acute infarct, with post-contrast enhancement of left basal ganglia lesion.
Case 1

- Working Dx: bilateral basal ganglia acute infarct due to vasculitis, ? cause (primary inflammation or secondary to infection)
- LP (D5): OP 9.2 cm water
  1. CSF TCC: 210 X10^6/L (lymphocytic pleocytosis 93%)
  2. CSF protein 1.59 g/L, CSF/serum glucose 4.7/7.3
  3. CSF Gram smear -ve, AFB smear -ve, TB-PCR -ve
  4. CSF viral PCR panel: T/F
- sputum AFB smear and TB-PCR both -ve
Case 1

- microbiologist consulted, in view of:
  1. *immunosuppressive state*
  2. *pneumonitis change on PET-CT*
  3. *respiratory Sx*
  4. *CSF lymphocytic pleocytosis + raised CSF protein*

- started empirical anti-TB Rx (D7): RIPE and iv Dexamethasone standard regime

- azathioprine stopped
Case 1

- D9: CSF PCR VZV DNA positive (serum/CSF VZV IgG not checked)
- iv Acyclovir 10 mg/kg Q8H for VZV meningitis/vasculitis
- dysarthria gradually resolved, buttock pain & LL numbness ↓
- 1 wk later, Dexamethasone reduced to 4 mg Q8H
- LP: CSF TCC 26 (L 92%) prot 0.5 g/L, glu 3.3 mmol/L (blood 4.9), PCR MTB -ve, PCR VZV -ve
- Dexamethasone ↓ to 4 mg BD 3 d later, anti-TB drugs stopped
- iv Acyclovir X 14 d, prednisolone tailed down to 12.5 mg daily
- oral Valacyclovir initiated
VZV infection

- VZV: exclusive human neurotropic alphaherpesvirus
- primary infection produces varicella (水痘)
- latent in cranial nerve, ganglia, dorsal root and autonomic ganglionic neurons
- reactivate to produce herpes zoster, and travels transaxonally to cerebral arteries where nerve terminates in the adventitia → inflammation → vascular remodeling → stroke (VZV vasculopathy)

Panel: Neurological complications associated with either varicella or herpes zoster

**Primary infection (varicella, chicken pox)**
- Acute cerebellar ataxia
- AIDP (Guillain-Barré syndrome) and AIDP varients
- Reye’s syndrome
- Myelitis
- Optic neuritis
- Meningitis and encephalitis
- Vasculopathy

**Reactivation (herpes zoster, shingles)**
- AIDP (Guillain-Barré syndrome)
- Myelitis
- Optic neuritis
- Meningitis and encephalitis
- Vasculopathy
- Focal motor weakness
- Ramsay-Hunt syndrome
- Post-herpetic neuralgia
Pathophysiology of VZV vasculopathy

I: intima, M: media, A: adventitia

- **infected cerebral arteries:**
  1. thickened intima composed of myofibroblasts, disrupted internal elastic lamina, paucity of smooth muscle cells
  2. inflammatory cells (primarily CD4+, CD8+ T cells & macrophages) present predominantly in adventitia, lesser degree in luminal surface of thickened intima
  3. early VZV vasculopathy: striking number of neutrophils in adventitia
  4. virological studies of intracerebral arteries (pts died of VZV vasculopathy) reveal inclusion bodies, multinucleated giant cells, herpes virions, VZV DNA & antigens
  5. both large & small arteries affected (70%), small arteries (37%), large arteries (17%)

Maria Nagel, Dallas Jones, Ann Wyborny, Journal of Neuroimmunology, 2017
Overlap features between VZV vasculopathy and giant cell arteries (GCA)

1. Gilden et al., Neurol Neuimmunol Neuroinflamm 2016
VZV vasculopathy: C/F, TIA/stroke

- TIA or stroke in elderly with Hx of zoster or children with varicella: alert to VZV vasculopathy
- mostly within 6 wks post-herpes zoster
- median interval for stroke after varicella is 4 m
- less frequent p/w SAH or ICH (ruptured aneurysm), rarely CVT
- may develop severe headache, cognitive impairment, confusion or unsteadiness
- adults often protracted clinical course (waxing & waning for 6-12 m, good response to anti-viral Rx)
- multiple reports: protracted disease >1 yr
Neuroimaging of VZV vasculopathy

- CT/MRI: single or multiple areas of ischemia/infarction in distribution of large/small arteries (often both)
- Multifocal VZV vasculopathy: lesions at gray-white matter junctions along with deep seated & cortical infarctions common
- High resolution MR: various patterns of stenosis, vessel wall thickening & enhancement, pred in terminal ICA & M1 of MCA
- FU after Rx: improvement of stenosis, reduced enhancement & vessel wall thickening (see left image)

Maria Nagel and Don Gilden Curr Neurol Neurosci Rep 2016
Neuroimaging of VZV vasculopathy: formation of intracerebral aneurysms

Maria Nagel and Don Gilden Curr Neurol Neurosci Rep 2016
VZV vasculopathy: Dx & Rx

- suspected in subjects, esp IC, who had a stroke or aneurysm with:
  1. recent varicella/herpes zoster
  2. recurrence of unclear cause with or without a rash
  3. unclear etiology & absence of stroke risk factors
- LP: CSF for VZV antibodies & DNA
- Rx: IV acyclovir 10-15 mg/kg for 14 d
- recurrent disease: second course (IV acyclovir) may be needed, particularly in IC pts, followed by oral antiviral for several m
- histological specimen often demonstrate arterial inflammation, many centers administer concomitant Prednisone 1 mg/kg from D1-5 with 14 days’ Acyclovir
<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
<th>Prognosis</th>
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<tbody>
<tr>
<td>Acute cerebellar ataxia</td>
<td>Intravenous aciclovir</td>
<td>Excellent</td>
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<tr>
<td>AIDP</td>
<td>Plasmapheresis, intravenous Ig</td>
<td>Excellent</td>
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<tr>
<td>Reye’s syndrome</td>
<td>Decreasing increased intracranial pressure</td>
<td>Permanent neurological deficit or death in up to 30% of patients</td>
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<tr>
<td>Myelitis</td>
<td>Aciclovir</td>
<td>Excellent</td>
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<tr>
<td>Optic neuritis</td>
<td>Aciclovir and intravenous steroids</td>
<td>Unknown</td>
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<tr>
<td>Meningitis</td>
<td>None</td>
<td>Usually favourable</td>
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<tr>
<td>Large vessel arteritis</td>
<td>Intravenous aciclovir</td>
<td>Up to 25% mortality</td>
</tr>
<tr>
<td>Small vessel vasculopathy</td>
<td>Intravenous aciclovir</td>
<td>Usually unfavourable</td>
</tr>
<tr>
<td>Focal motor weakness</td>
<td>Oral aciclovir</td>
<td>Good</td>
</tr>
<tr>
<td>Ramsay-Hunt syndrome</td>
<td>Oral aciclovir</td>
<td>Excellent</td>
</tr>
<tr>
<td>Oral famiclovir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-herpetic neuralgia</td>
<td>Difficult (see text)</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

Table 2: Treatment and prognosis of neurological syndromes associated with VZV infection
<table>
<thead>
<tr>
<th>Preparations</th>
<th>Dosage</th>
<th>Indications</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciclovir</td>
<td>Intravenous, oral, topical, ophthalmal 10 mg/kg three times daily for 10-14 days. Dose should be adjusted with impaired renal function</td>
<td>First line for HSE, Herpes zoster</td>
<td>Nephrotoxicity, neurotoxicity, phlebitis, vesicular eruptions, increased aminotransferase concentrations</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>Intravenous, oral 40 mg/kg twice or three times daily for 2-3 weeks. Should be reduced in patients with impaired renal function</td>
<td>Aciclovir-resistant HSE</td>
<td>Nephrotoxicity, electrolyte imbalance (especially hypocalcaemia), penile ulcerations, seizures</td>
</tr>
<tr>
<td>Valaciclovir</td>
<td>Oral 1000 mg every 8 h for 7 days</td>
<td>Herpes zoster</td>
<td>Similar to aciclovir, gastrointestinal complaints, neutropenia</td>
</tr>
<tr>
<td>Famiclovir</td>
<td>Oral 500 mg every 8 h for 7 days</td>
<td>Herpes zoster</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Brivudine</td>
<td>Oral, topical 125 mg once daily for 7 days</td>
<td>Herpes zoster</td>
<td>Gastrointestinal complaints, hypersensitivity, proteinurea, glucosurea</td>
</tr>
</tbody>
</table>

Table 3: Medications in use for neurotropic herpes virus infections
CNS infection: Diveristy in micro-organisms

Panel 2: Common infectious causes of meningitis in resource-poor settings

**Bacterial**
- *Streptococcus pneumoniae* (commonest cause worldwide; associated with HIV infection)
- *Haemophilus influenzae* type B
- *Neisseria meningitides* (serogroups A, W-135, C, and X cause epidemics in Africa; serogroups B and C are more common in Europe, North America, Australia, and east Asia)
- *Streptococcus suis* (commonest cause of bacterial meningitis in southeast Asia)
- *Staphylococcus aureus* (uncommon)
- Group B streptococci (common cause in neonates)
- *Listeria monocytogenes* (neonates, elderly people, and immune compromised)
- *Enterobacteriaceae* spp (neonates, elderly people, and immune compromised)
- Non-typhi *Salmonella* sp (patients in Africa who are infected with HIV)
- *Mycobacterium tuberculosis* (more common with HIV infection)
- *Treponema pallidum*

**Fungal**
- *Cryptococcus neoformans* (advanced HIV infection)

**Parasitic**
- *Angiostrongylus cantonensis* and *Gnathostoma spinigerum* (eosinophilic meningitis in southeast Asia)
- *Toxocara canis* (worldwide)

**Viral**
- Herpes viruses (herpes simplex and varicella zoster)
- Enteroviruses
CNS infection: Diversity in micro-organisms

Orientalia, rickettsia, and leptospira pathogens as causes of CNS infections in Laos: a prospective study

Sabine Dittrich, Sayaphet Rattanavong, Sue J Lee, Phonepasith Panyanivong, Scott B Craig, Suhella M Tulsiani, Stuart D Blacksell, David A B Dance, Audrey Dubot-Pérès, Amphone Sengduangphachanh, Phonelavanh Phoumin, Daniel H Paris, Paul N Newton

Findings 1051 (95%) of 1112 patients who presented had CSF available for analysis, of whom 254 (24%) had a CNS infection attributable to a bacterial or fungal pathogen. 90 (35%) of these 254 infections were caused by O tsutsugamushi, R typhi/Rickettsia spp, or Leptospira spp. These pathogens were significantly more frequent than conventional bacterial infections (90/1051 [9%] vs 42/1051 [4%]; p<0.0001) by use of conservative diagnostic definitions. CNS infections had a high mortality (236/876 [27%]), with 18% (13/71) for R typhi/Rickettsia spp, O tsutsugamushi, and Leptospira spp combined, and 33% (13/39) for conventional bacterial infections (p=0.076).

Interpretation Our data suggest that R typhi/Rickettsia spp, O tsutsugamushi, and Leptospira spp infections are important causes of CNS infections in Laos. Antibiotics, such as tetracyclines, needed for the treatment of murine typhus and scrub typhus, are not routinely advised for empirical treatment of CNS infections. These severely neglected infections represent a potentially large proportion of treatable CNS disease burden across vast endemic areas and need more attention.
CNS infection: Diversity in

- causative micro-organisms
- clinical manifestations
- complications
Thank you