The Clock is Ticking in Europe; cooperation, cross-reactions and co-infection...

A Case from The Royal Sussex County Hospital

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Case: Presenting to Medical FY1 on-call from A&E

- 33yo Caucasian male
- PC:
  - Diplopia and photophobia
  - Headache – severe for 3/7
  - Lethargy and myalgia
- HPC:
  - GP → eye hospital → A&E
  - 2/52 worsening headache
  - 2x LOC (associated with ETOH)
Admission Clerking

• PMH:
  – Depression, Chronic Fatigue, Lactose intolerant

• DH: NKDA
  – Citalopram OD, Amitriptyline ON

• SH:
  – Lives with his parents, Smoker (roll-ups – 1 pouch /wk) + occasional cannabis
  – ETOH <21 units per week
Travel History

- Recent cycling trip
- Holland – Sweden – Lithuania
- Slept on a hammock
- Drank from rivers
- Multiple tick bites
- >30 attached ticks
- No rash

University of Nebraska, Omaha. maps.unomaha.edu/
On Examination

- Tall, slim and tanned
- Lying still
- Photophobia
- Hyperacusis
- Obs:
  - Temp - 37.8°C
  - HR 110 bpm
  - BP 130/70
  - RR 18 bpm
  - O₂ 97% RA

VBG:
- BM 5.2mmol/L
- Lactate 1.6 mmol/L
On Examination

- Chest – clear
- CVS – I+II+O
- Abdo – SNT
- Nil rash seen
- Slight erythema left knee – no effusion
- Intolerant of pupillary examination
- Neuro: CN 1-12- diplopia and hyperacusis, otherwise NAD.
  - PNS: 4/5 lower limb, hyper-reflexia LL, tone normal.
  - Bladder and bowel reported as normal
Initial Investigations and Management

• Bloods
  – U&E, FBC, LFT – NAD
  – CRP 2.9mg/L
  – Viral throat swab – NAD
  – HIV, Hep screen, Lyme, CMV, EBV sent

• Urine: + ketones
Initial Investigations and Management

- IV Fluid, paracetamol and PRN codeine
- Ceftriaxone 2g IV
- CT head and LP
  - CTH NAD
  - CSF: (clear and colourless)
    - Protein: 712.0 mg/L (Serum: 67 mg/L)
    - CSF glucose 3.0 mmol/L (CBG 5.2 mmol/L)
    - WCC: 1
    - RCC: 371 (Xanthochromia –ve)
    - CSF viral panel negative for HSV 1+2, VZV, Enteroviruses, Mumps and parechovirus RNA
Differentials

• Meningitis – Bacterial/Viral
• Encephalitis
 +/- associated HIV/immuno-suppression

...Discussed with on-call ID SpR and Consultant...

• Neuroborreliosis
• Tick Borne Encephalitis

Felt to be clinically predominantly meningitic rather than Encephalopathic
  – Ceftriaxone to be continued to cover Lyme and *N. meningitis*
  – Hold Aciclovir given clinical presentation
Admitted under ID

Day 2:

Seen by ID Consultant:

– No tick borne encephalitis vaccination pre-travel
– No sexual contacts >1 year. Never IVDU
– Swinging pyrexia up to 39°C – Blood Cultures taken
– Further virology tests on CSF and MRI brain (NAD)

• **Bloods**: CRP 49, WCC 19 (Neut 16)
• **ECG** – up-slanting of ST segment. No chest pain/SOB. Troponin <3mcg/L.
Progression

**Blood Cultures** – no growth

**Throat swabs** – NAD.

**CSF viral panel** – NAD, reference lab report awaited

**Day 5:**
- Apyrexial 24 hours
- Remains photophobic and hyperacoustic
# Reference Lab - Lyme Serology

<table>
<thead>
<tr>
<th></th>
<th>IgM</th>
<th>IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B. burgdorferi</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Borrelia Osp17</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Borrelia V1sE</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Borrelia Lineblot</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Borrelia P41</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Borrelia OspC</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Borrelia C6 EIA</strong></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Epstein-Barr virus (EBV)</td>
<td>+ (trace)</td>
<td>+</td>
</tr>
<tr>
<td>Japanese Encephalitis</td>
<td></td>
<td>+ (1/32)</td>
</tr>
<tr>
<td>Tick Borne Encephalitis</td>
<td></td>
<td>+ (1/1000)</td>
</tr>
<tr>
<td><strong>EBV Viral PCR</strong></td>
<td></td>
<td>Not detected</td>
</tr>
<tr>
<td><strong>CMV</strong></td>
<td></td>
<td>Not detected</td>
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</tbody>
</table>
Serology

• Lyme serology felt to be consistent with recent infection
  – Treated as Neuroborelliosis → PICC inserted for OPAT

• Japanese Encephalitis and EBV likely positive as result of cross reactivity.

Progression

• Consistent with Tick Borne Encephalitis
• Treated as Lyme encephalitis +/- pericarditis
• 28 days Ceftriaxone
• **CSF Lyme: result on day 13: CSF Lyme negative**
• Slow improvement:
  – lethargy
  – persistent hyperacausis
  – hypereflexia and hypertonia
## Tick Borne Encephalitis (TBE) and Lyme

<table>
<thead>
<tr>
<th></th>
<th>TBE</th>
<th>Lyme (<em>Borrelia burgdorferi</em>)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vector</strong></td>
<td>Ixodes Ricinus</td>
<td>Ixodes Ricinus</td>
</tr>
<tr>
<td><strong>Endemic Area</strong></td>
<td>non-endemic to UK (Europe, Siberia, Far East)</td>
<td>Endemic to UK</td>
</tr>
<tr>
<td><strong>Host</strong></td>
<td>Mammals</td>
<td>Mammals (deer, dogs etc)</td>
</tr>
<tr>
<td><strong>Pathogen</strong></td>
<td>Flavivirus (3 subtypes)</td>
<td>Spirochete</td>
</tr>
</tbody>
</table>
| **Clinical Features** | • Viremic phase 66% (early) – nonspecific; fever, malaise  
                   | • Neurological involvement (phase 2) – meningo/encephalitis | • Erythema migrans 70%  
                   |                                                                 | • Lyme arthritis, carditis  
                   |                                                                 | • Neuroborreliosis  
                   |                                                                 | • Acrodermatitis chronica atrophicans |
| **Management**      | There is no active treatment available           | doxycycline, amoxicillin, ceftriaxone        |


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*Picture via WebMD*
Tick Borne Encephalitis (TBE) and Lyme

TBE:
- Serology: CSF IgM ELISA positive in neuroinvasive stage (other flavivirus’ cross react)
- Viral RNA PCR +ve in initial illness phase
- Viral RNA PCR –ve once neurological symptoms develop

Lyme:
- NICE previously: Patients with EM do not require serological testing¹
- Serology (2-tiered testing) – C6-ELISA then confirmation with Western blot
- False +ve ELISA
- PCR yield better results from tissue samples

Common Vector

• Common vector - co-infection
• Numerous bites vs single bite multi-carrier tick
• Literature search of co-infection:
  – 1.7% co-infected patients¹
  – Up to 30% of ticks co-infected with multiple pathogens²
    • 6% specific to TBE/Borrelia³
  – Ticks with ≥ 6 distinct infections⁴
• Patient with >30 bites – Multi-carrier tick theory discussed with BSUH Professor of Entomology – bite burden indicated likely 2 distinct inoculations

3. Bristol University Tick ID. www.bristoluniversitytickid.uk
Vaccination against TBE

- Many European countries are reporting increased incidence of TBE yearly, due to extended biting seasons due to temperate winter conditions.

- UK Vaccine *TicoVac (Masta ltd)* – 3 dose vaccine (1,3,12mnths)
  - Not suitable for Gentamicin/Neomycin allergy

- Vaccination programs against TBE are present in several counties including France, Austria, Switzerland and Germany.

- European approved inactive vaccine – 3 dose regime

- Up to 95% effective (less effective in older age groups)

Conclusions

• Clinical case of co-infection with TBE and Borrelia
  – Mixed central and peripheral symptoms

• Difficulties in diagnosing co-infection

• Concerns regarding serological cross reaction

• Clinicians should consider co-infection whenever suspecting a single tick-borne diagnosis
Questions and Thanks

Thanks to co-authors and BSUH Team:
• Dr Gill Jones
• Dr Erica Pool
• Dr Dan Agranoff