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BIRMINGHAM, ICC

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

A Case from The Royal Sussex County Hospital

Rosenbaum L[1], Pool E[2], Agranoff D[3], Jones G[3]

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[1] Kingston Hospitals NHS Foundation Trust
[2] University College London
[3] Brighton and Sussex University Hospitals NHS Trust

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

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- 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)

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Admission Clerking

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- 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

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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
  - O_2 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

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

- Urine: + ketones

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Initial Investigations and Management

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- 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: 67mg/L)
    - CSF glucose 3.0mmol/L (CBG 5.2mmol/L)
    - WCC: 1
    - RCC: 371 (Xanthochromia –ve)
    - CSF viral panel negative for HSV 1+2, VZV, Enteroviruses, Mumps and parechovirus RNA

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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

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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.

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Progression

Blood Cultures – no growth

Throat swabs – NAD.

CSF viral panel – NAD, reference lab report awaited

Day 5:

- Apyrexial 24 hours
- Remains photophobic and hyperacustic

Reference Lab - Lyme Serology

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	IgM	IgG
B.burgdorferi	+	+
Borrelia Osp17	+	+
Borrelia V1sE	-	+
Borrelia Lineblot	+	+
Borrelia P41	+	
Borrelia OspC	+	-
Borrelia C6 EIA	+	
Epstein-Barr virus (EBV)	+ (trace)	+
Japanese Encephalitis		+ (1/32)
Tick Borne Encephalitis		+ (1/1000)
EBV Viral PCR – Not detected		
CMV – Not detected		

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Serology

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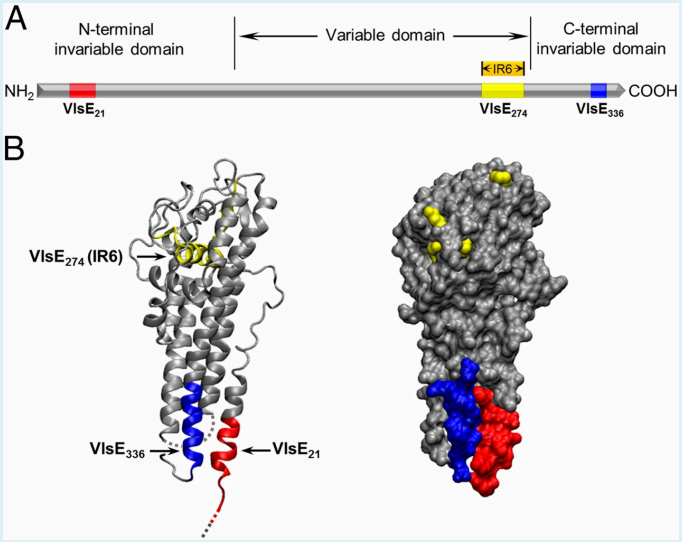
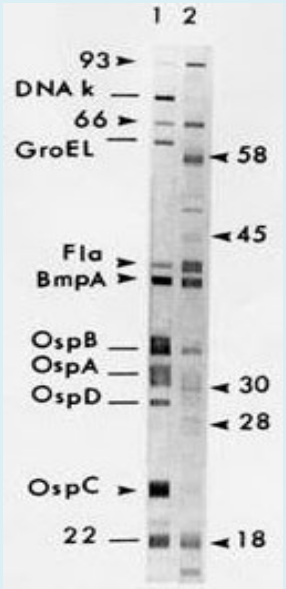
- Lyme serology felt to be consistent with recent infection
  - Treated as Neuroborelliosis → PICC inserted for OPAT

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





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Jacek, E., et al (2015). J Immunol 196(3), pp.1036-1043.

https://www.cdc.gov/lyme/diagnosistesting/labtest/twostep/westernblot/index.html

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 hyperacusis
  - hypereflexia and hypertonia

Tick Borne Encephalitis (TBE) and Lyme

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	TBE	Lyme (*Borrelia burgdorferi*)
Vector	Ixodes Ricinus	Ixodes Ricinus
Endemic Area	non-endemic to UK (Europe, Siberia, Far East)	Endemic to UK
Host	Mammals	Mammals (deer, dogs etc)
Pathogen	**Flavivirus** (3 subtypes)	**Spirochete**
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


Picture via WebMD

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- Fischer M, Rabe IB, Rollin PE (2017). Tickborne Encephalitis. www.cdc.gov
- Public Health England. The Green Book. www.gov.uk/

Tick Borne Encephalitis (TBE) and Lyme

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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 testing[1]
- Serology (2-tiered testing) – C6-ELISA then confirmation with Western blot
- False +ve ELISA
- PCR yield better results from tissue samples

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[1]British Infection Association (2011) Journal of Infection 59(329-338). www.cks.nice.org.uk

Common Vector

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- Common vector - co-infection
- ?numerous bites ?single bite multi-carrier tick
- Literature search of co-infection:
  - 1.7% co-infected patients [1]
  - Up to 30% of ticks co-infected with multiple pathogens[2]
    - 6% specific to TBE/ Borrelia[3]
  - Ticks with ≥ 6 distinct infections[4]
- Patient with >30 bites– Multi-carrier tick theory discussed with BSUH Professor of Entomology – bite burden indicated likely 2 distinct inoculations

Picture via Bristol University Tick ID

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1. Bröker, M. (2011). *Zoonoses and Public Health*, 59(3),pp.176-180.
2. Raileanu, C., et al. (2017). *PLOS Neglected Tropical Diseases*, 10(3), p.e0004539.
3. Bristol Univerasity Tick ID. www.bristoluniversitytickid.uk
4. Swanson, S., et al. (2006). *Clin Micro Rev*, 19(4), pp.708-727

Vaccination against TBE

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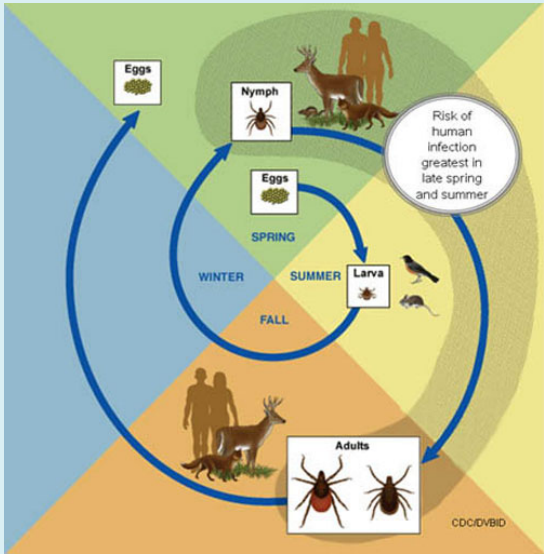
- Many European countries are reporting increased incidence of TBE yearly, ?due to extended biting seasons due to temperate winter conditions.
- UK Vaccine *TicoVac (Masta ltd)* – 3 dose vaccine (1,3,12mnths)
  - Not suitable for Gentamicin/Neomycin allergy
- Vaccination programs against TBE are present 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)



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CDC. 2017. Lifecycle of Blacklegged Ticks. www.cdc.gov

Conclusions

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- 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

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Questions and Thanks

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