Tick-Borne Encephalitis

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Case study 1

45M, store manager, previously fit and well, been fishing in the Czech Republic in May Early June – sore throat, temp. 37.5, some headache and myalgia

WBC 2.8, Plt 110
CRP 20 (0-5 mg/L)
ALT 80 (0-40 IU/L), GTT 45 (0-40 IU/L)
After 5 days back to normal
Case study 1

Mid June – spiking temps T 38-39 for a few days, severe headache, photophobia, nausea/vomiting, tremor upper limbs and eyelids

Exam: mild neck stiffness, intention tremor, poor finger-to-nose coordination/dysmetria

Recalls a tick bite end May
Not vaccinated against tick borne encephalitis (TBE)
Case study 1

Admission – WBC 10.2, Plt 250
ALT 40 (0-40 IU/L), CRP 10 (0-5 mg/L)
TBE serology negative IgM, IgG
Management plan?
Case 1

CT head negative

LP: protein 0.85 (0-0.45 g/L), glu 5.6 mmol/L, lactate 2.1 mmol/L, leukocytes 152 (0-3), 60% lymphocytes,
Case study 1
End June: no more fever, persisting headaches, better coordination, poor concentration

F/U serology TBE: positive IgG, positive IgM

End December: difficult to concentrate at work despite phased return, frequent headaches, sensitive to noise and light, mild tremor, erectile dysfunction
BIPHASIC COURSE OF TICK-BORNE ENCEPHALITIS

1. VIRAEMIA

2. NEUROLOGICAL IMPAIRMENT

Fever

IgM

IgG

INCUBATION

End May  June  July

0  1  2  3  4  5  6  7

WEEKS

End May

June

July

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Case study 1

End December: fatigue, difficult to concentrate at work, regular headaches, sensitive to noise and light, irritability, mild tremor, erectile dysfunction

1 miserable year of life
Post-encephalitic syndrome

Disease burden: DALY 3.1 years per case

2% acute illness, 5% mortality, 93% disability

Šmit R, Postma MJ, 2015, PlosONE 10(12):e0144988
Confirmed TBE cases in České Budějovice Hospital

C Bud ID unit (regional pop. 450k)

2016: 62
2017: 79
2018: 76

Austria (national pop. 8.7M)

2014: 81
2015: 79
2016: 95

Europe (ECDC) notifiable disease
2500 cases/year
Total 7-10,000 cases/year
Endemic regions in Europe 2012

Endemic regions in Europe 2016

Tick-borne encephalitis mean notification rate per 100,000 population, 2012–2016

- Data not available
- No surveillance
- Not included

Statistical level
- Country
- NUTS 2
- NUTS 3
Seasonal incidence of TBE

Hard ticks

*Ixodes ricinus* – central Europe

*Ixodes persulcatus* – Far East, Siberia

Rodents, small mammals

In Europe: 0.1 – 3% ticks infected

risk of infection after a tick bite 1:25 – 1:1,000

Brain inflammation

Astrocytes and microglia - production of TNF-a, IFN-a, IL-1b, IL-6, IL-8, IL-12, IFN-g, IP-10

Neuronophagia
Endothelial activation
Perivascular infiltrates
Activated microglia
Histiocyte nodules
Cytotoxic T cell infiltration

Breakdown of blood brain barrier due to inflammation

Růžek D, Antiviral Research 164 (2019) 23–51
Case 2

66 years old farmer
Presented in September 2017
3 days fever, headache
1 day slightly confused and generally weak

HDU – weakness of upper limbs and slurred speech
Next day unable to cough and swallow
Case 2

66 years old farmer
Day 2 of admission intubated, ventilated, early tracheostomy, off sedation
Weaning of ventilator in 8 days
Unable to swallow, poor coughing
Left diaphragm palsy
Proximal bplegia of upper limbs
Weakness of lower limbs
Case 2

66 years old farmer
October – March 2018 – intensive care
tracheostomy, parenteral nutrition, PEG feed
Repeat chest infections – bronchoscopic lavage
of the left bronchi
General wasting
Fully alert throughout
Died of progressive respiratory failure 6 months
after admission
Vaccination

Vaccination uptake in Austria (1 shot, complete course 53%)

TBE incidence rate in CZ (where vaccination cover <20%)

TBE incidence rate in Austria

Heinz FX, Field effectiveness of vaccination against tick-borne encephalitis *Vaccine*. 2007 Oct 23;25(43):7559-67
Vaccine

Highly purified inactivated whole virus vaccines (Germany, Austria, Russia x2), paediatric version

Scheme month 0/1/12, boosters every 3-5 yrs
Accelerated scheme day 0/14/150 or 0/7/21 d

Effective protection (>90%) 1 week after 2\textsuperscript{nd} dose
Efficacy after three doses 99%
Antibodies protective up to 10 years in >90%

Risk assessment

Factors of the environment
Region, country and region
Season (high risk from April to November);
Lower altitude (<1500 m above the sea level)

Factors of the individual
Outdoor activity - extent
Duration of stay
Higher age/comorbidities

What we would like to know in diagnostics?

Urinary PCR in the viraemic/neurological phase

Functional MRI

Cytokine assay to predict possible disability

Host genomics to predict disease severity

What we know in therapy?

Treatment and prophylaxis

No specific treatment for tick-borne encephalitis exists.

There is no curative therapy for TBE, so supportive

7.3 Therapy and Prophylaxis

The treatment for TBE is currently symptomatic since no

Studahl et al.
Drugs. 2013,

Lindquist,
Lancet 2008

Mansfield et al.
Journal of General Virology 2009
What we would like to know in therapy?

In Austria/Germany/Baltic states: no corticosteroids

Czech practice: selected cases with refractory headache/hyperpyrexia, paresis, somnolence, or other signs of raised intracranial pressure

Ethical dilemma about RCT

In supportive Rx despite diagnosis: corticosteroids have antiedematous, antiemetic, and antipyretic effect. Effective in refractory hiccups.

What we would like to know in F/U post discharge?

Bedrest vs. Early neurorehabilitation

Cognitive training
Goal setting
Coping strategies
Patient support groups
EEG – Biofeedback

Mild learning disability - in children

Steffen R. Ticks and Tick-borne Diseases, Volume 10, 1, January 2019, Pages 100-110
Summary – what we know

**Epidemiology** – viral illness by ticks, central and eastern Europe, Russia, northern China

**Clinical presentation** – biphasic course, low mortality, significant long term disability, potential of co-infection

**Diagnostics** – delayed serology, cross reaction

**Therapy** – symptomatic, supportive, specialized centres

**Prevention** – effective vaccination (+repellents)

Summary – what we would like to know

**Epidemiology** – new regions affected

**Clinical presentation** – preventing development of severe neurological disability, immunosuppressed

**Diagnostics** – TBEV PCR in urine, cytokine/T cell profile

**Therapy** – immunomodulation, incl. steroids, directly acting drugs (HepC is a flavivirus)

**Neurorehabilitation**

**Prevention** – increase vaccination rate, travellers
Short review, summary including risk assessment and vaccination schedules

Chrdle A, Chmelík V, Růžek D.
Tick-borne encephalitis: What travelers should know when visiting an endemic country.

Extensive review including current research questions

Ruzek D¹, Avšič Županc T², Borde J³, Chrdle A⁴, Eyer L⁵, Karganova G⁶, Kholodilov I⁷, Knap N², Kozlovskaya L⁶, Matveev A⁸, Miller AD⁹, Osolodkin D¹⁰, Överby AK¹⁰, Tikunova N⁸, Tkachev S⁸, Zajkowska J¹¹
Tick-borne encephalitis in Europe and Russia: Review of pathogenesis, clinical features, therapy, and vaccines.

Consensus guideline for diagnosis and management – TBE Working Group

Taba P¹, Schmutzhard E², Forsberg P³, Lutsar I⁴, Ljøstad U⁵, Mygland Å⁵, Levchenko I⁷, Strle F⁸, Steiner I⁹.
EAN consensus review on prevention, diagnosis and management of tick-borne encephalitis.