Hepatitis E and Neurological disease

Harry Dalton
**Virology of HEV**

*Hepeviridae* viruses infect mammals, birds and fish.

Strains infecting humans belong to the *Orthohepevirus* genus, species A.

Species A comprises 8 genotypes.

- **GT 1**
  - Only infect humans
  - Faecal–oral spread via contaminated water
  - Large outbreaks
  - Brief, self-limiting
  - Never chronic
  - High mortality in pregnancy (25%)

- **GT 2**

- **GT 3**
  - Endemic in animal species: eg, pigs and wild boar
  - Zoonotic infections in humans
  - High-income countries
  - China: GT 4 most common
  - Japan GT3 & GT4
  - S. America: GT 3 only

- **GT 4**
  - Have only been reported in wild boar

- **GT 5**

- **GT 6**

- **GT 7**
  - GT 7 identified in patient regularly consuming camel meat and milk
  - Have since been identified in camels

- **GT 8**

**EASL CPG HEV. J Hepatol 2018**
HEV in developing countries

- Major health issue
- Genotypes 1 & 2
- Faeco-oral route via infected water
- Affects young adults
- Mortality in pregnant women 25%
HEV in developed countries: received wisdom

- Seen in travellers
- Of little relevance in developed countries
acute HEV Gt 3 (and 4)

- Commonest cause acute viral hepatitis in many European countries

- ? ≥2 million locally acquired HEV infections in Europe per year
  - Mostly zoonotic, Pigs primary host

- Mostly Gt 3 (occasionally Gt4)
  - Locally acquired, travel history irrelevant
  - M:F ratio 3:1; median age 63 years\(^1\)
  - Self limiting hepatitis
  - Deaths in patients with pre-existing chronic liver disease
  - No deaths in pregnancy

Acute HEV3: symptoms

**COMMON**
- Jaundice
- Anorexia
- Lethargy
- Abdominal pain
- Vomiting
- Fever
- Myalgia

**LESS COMMON**
- Pruritis
- Weight loss
- Headaches
- Arthralgia
- Neurological
- No symptoms

*Dalton et al EJGH 2008, Woolson et al APT 2014*
Chronic HEV infection: immunosuppressed

- Chronic HEV3 infection in transplant patients
  - No symptoms, anicteric, ALT 200-300IU/L
  - 10% cirrhotic in 2 years

- Prevalence of chronic HEV
  - High in French transplant centres
  - Other European transplant centres: 1-2%

Kamar et al NEJM 2008
Pas et al EID 2012
Koning et al J Heart Lung Tran 2013
Moal et al JMV 2013
Halac et al Gut 2012
Pischke et al Am J Transpl 2012
Source and route of infection

Dalton et al Lancet Inf Dis 2008
Source and route of infection

Vocational exposure: vets, farmers, processing and retail staff

Pig

Abattoir Effluent

Slurry

Run-off from outdoor pig farms

Pasture

Crops

Watercourses

Crops via irrigation

Water-based recreation

Abstract drinking

Human sewage, Floods

Blood Transfusion

Other mammals

Man
HEV3: incidence varies between & within countries & over time

- UK: 0.2%  
  Ijaz et al 2009 JClinVirol  
  Ijaz et al JID 2014

- Netherlands: 1.1%  
  Slot et al Eurosurv 2013

- SW France: 3.2%  
  Abravenal et al JID 2014
• England and Wales:
  – 869 lab confirmed cases of HEV (2014)

• England:
  – incidence HEV: >100,000/yr

HEV seroprevalence: varies within countries

Mansuy et al 2016 Hepatology
HEV incidence varies over time

Adlhoch et al JCV 2016
HEV

‘Hot spots’ in Europe

Thom et al EuroSurveill 2018
Niederhauser et al Eurosurv 2018
Westhölter et al J Hepatol 2018
Bura et al IntInfDis 2017
Mansuy et al Hepatology 2016
Zaaijer Hepatology. 2015
Müller et al TrMedHemo 2015
Lucarelli et al EuroSurveill 2016
Grabarczyk et al Transfusion 2018
<table>
<thead>
<tr>
<th>Country</th>
<th>Blood donors HEV RNA positive</th>
<th>HEV IgG seroprevalence</th>
<th>Assay</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
<td>Gallian et al, 2014</td>
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<tr>
<td>Midi-Pyrénées</td>
<td>1:1595</td>
<td>52%</td>
<td>Wantai Genelabs</td>
<td>Mansuy et al, 2011</td>
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<tr>
<td></td>
<td></td>
<td>16%</td>
<td></td>
<td>Mansuy et al, 2008</td>
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<td>Japan</td>
<td>1:1781</td>
<td></td>
<td></td>
<td>Fukuda et al, 2004</td>
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<tr>
<td>Germany</td>
<td>1:1200 1:4525</td>
<td>29.5%</td>
<td>Wantai</td>
<td>Vollmer et al, 2012</td>
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<td></td>
<td></td>
<td>27.0%</td>
<td>Mikrogen</td>
<td>Baylis et al, 2012</td>
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<td></td>
<td></td>
<td>4.5%</td>
<td>MP diagnostics</td>
<td>Wenzel et al, 2013</td>
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<tr>
<td>Netherlands</td>
<td>1:2671</td>
<td>27.0%</td>
<td>Wantai</td>
<td>Slot et al, 2013</td>
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<tr>
<td></td>
<td></td>
<td>1.1%</td>
<td>Abbott</td>
<td>Zaaijer et al, 1993</td>
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<tr>
<td>Sweden</td>
<td>1:7986</td>
<td>9.2%</td>
<td>Abbott</td>
<td>Baylis et al, 2012</td>
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<td></td>
<td>Olsen et al, 2006</td>
</tr>
<tr>
<td>England</td>
<td>1:2848 1:7000</td>
<td>12.0%</td>
<td>Wantai</td>
<td>Hewitt et al, 2014</td>
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<tr>
<td></td>
<td></td>
<td>5.3%</td>
<td>Abbott</td>
<td>Ijaz et al, 2012</td>
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<td>Beale et al, 2011</td>
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<td></td>
<td>Bernal et al, 1996</td>
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<tr>
<td>Scotland</td>
<td>1:14520</td>
<td>4.7%</td>
<td>Wantai</td>
<td>Cleland et al, 2013</td>
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</table>
HEV RNA donor screening

- Universal screening:
  - Germany: summer 2019
  - Swiss: Nov 2018
  - UK: April 2017
  - NL: July 2017
  - Ireland: Jan 2016
HEV: extrahepatic manifestations

- Meningitis
- Thyroiditis
- Neuralgic amyotrophy
- Cryoglobulinemia
- Myocarditis
- Pancreatitis
- Glomerulonephritis
- Lymphoma/thrombocytopenia
- Arthralgia/myalgia
- Guillain-Barré syndrome

Enveloped viruses in the peripheral blood

Non-enveloped viruses being excreted in stool
HEV and neurological injury

- ~200 cases worldwide:
  - Guillain–Barré syndrome
  - Neuralgic amyotrophy
  - Meningoencephalitis
  - Myasthenia gravis
  - Miscellaneous
    - Bells Palsy, myositis, mononeuritis multiplex, vestibular neuritis

- Occurs in:
  - Acute and chronic HEV
  - Developed and developing countries

- Neurological symptoms and signs dominate clinical picture

Guillain-Barré Syndrome (GBS)

- Post infectious immune-mediated polyradiculopathy

- Infectious triggers:
  - Campylobacter: 35%
  - Unknown: 50%

- 30% abnormal liver function? Cause

Oomes et al Neurology 1996
HEV & Guillain-Barré syndrome

Case control study of Dutch patients with GBS (n=201)

- 5% of GBS have HEV infection (10/201, p=0.01 vs controls)

• Liver function tests:
  - Not jaundiced
  - Normal liver function n=3

• Outcome:
  - 1 required ventilation, 7 have significant disability at 6 months

van den Berg et al Neurology 2014
HEV and GBS

- Case control study of Bangladeshi patients with GBS (n=100)
  - 11% of GBS have HEV infection (HEV genotype 1, n=1)

HEV & meningoencephalitis

- 14 cases: Europe n=9, Asia n=4, USA n=1
- Immunosuppressed (n=5)
  - Ataxic syndrome
- HEV RNA (genotype 3) serum and CSF (n=6)
  - Quasispecies compartmentalisation
- LFTs modestly elevated
- Outcome variable: Worse in immunosuppressed

_Dalton et al Nature Neurol Rev 2016_
HEV & Neuralgic amyotrophy
(brachial neuritis, Parsonage Turner syndrome)

- LFTs abnormal in some patients, ? Cause

- Anglo/Dutch cohort study: 47 patients tested for HEV
  - 5 (10%) had HEV at the start of the illness
  - Age 30-40 years
  - Mildly abnormal liver function: ALT 100-300, normal bilirubin
  - 4 PCR positive: HEV genotype 3

Van Eijk et al, Neurology 2014
Neuralgic amyotrophy and HEV: Multi-centre international study

• Cornwall UK, Holland, Germany, Switzerland, France, Italy
• Retrospective study
• NA cases:
  • HEV +ve  n=57
  • HEV –ve  n=61
• Outcome measures:
  • Clinical phenotype & Outcome

Van Eijk et al, Neurology, 2017
Neuralgic amyotrophy and HEV: Multi-centre international study

<table>
<thead>
<tr>
<th></th>
<th>HEV +ve</th>
<th>HEV -ve</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51 (23-83 yrs)</td>
<td>44 (25-79)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male</td>
<td>82%</td>
<td>75%</td>
<td>NS</td>
</tr>
<tr>
<td>ALT</td>
<td>259 (12-2961)</td>
<td>23 (7-396)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Bilateral involvement</td>
<td>80%</td>
<td>8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phrenic/lumbar involvement</td>
<td>58%</td>
<td>10%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td>Variable</td>
<td>Variable</td>
<td>NS</td>
</tr>
</tbody>
</table>

Van Eijk et al, Neurology, 2017
Patients with acute non-traumatic neurological injury tested for HEV (n=464)

- Current HEV infection
  - IgM+, IgG+, PCR+ n=3
  - IgM-, IgG-PCR+ n=2

- Recent HEV Infection
  - IgM+, IgG+, PCR+ n=4

- Distant HEV infection
  - IgM-ve, IgG+, PCR+ n=152
  - IgM-ve, IgG-ve PCR+ n=302

- Never Infected with HEV

Den Bosch, the Netherlands n=83
Toulouse, France n=164
Cornwall and Plymouth, UK n=217

Dalton et al. Journal of Hepatology, 2017
<table>
<thead>
<tr>
<th>Acute neurological event</th>
<th>Number tested (n=)</th>
<th>HEV infection; n= (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuralgic amyotrophy</td>
<td>5</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>11</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>7</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>7</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cranial Nerve palsies</td>
<td>31</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Seizure(s)</td>
<td>44</td>
<td>3* (7%)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>170</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>68</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Migraine/headaches</td>
<td>51</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>12</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Myelitis</td>
<td>14</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>25</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>28</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
“Harry. Has this virus been misnamed?”

“These patients have profound neurological injury, but not much of a hepatitis”
HEV & neurological syndromes: evidence for causality

- Number and homogeneity of cases
  - Over time and geographical location
- Case-control data (GBS)  
  - Netherlands (HEV3) & Bangladesh (HEV1) & Japan  
  - van den Berg et al, Neurol 2014; Geurtsvankessel et al Clin Inf Dis 2013  
  - Fukae et al Neurol Sci 2016
- Intrathecal anti-HEV IgM synthesis  
  - Silva et al 2016
- HEV RNA  
  - Serum and CSF
- Resolution of neurological symptoms with viral clearance  
  - Dalton et al Ann Int Med 2010  
- Kernow C1p6  
  - Grows on a range of cell lines, including neurological
HEV & neurological syndromes: evidence for causality

HEV infects neurological cell lines:

Replication of full length HEV genotype 3 Kernow-C1 p6 strain in different neuronal and placental cell lines

HEV crosses blood brain barrier in mice:

eGFP-HEV

72 hrs
HEV burden of disease

Genotype 1 and 2

- 3 million cases/year
- 70,000 deaths

Genotype 3 and 4

- Unknown
- On going international study
HEV gt3 burden of disease: lab confirmed HEV cases (n=283)

outcome

• 69% admitted to hospital (1892 bed days)
• Liver failure n= 21
• Acute kidney injury n=28

• Neurological disease n=25
  – 50% long term residual symptoms

• 9 deaths (2.8%)
  – Liver failure n=7
  – Chronic HEV n=2

Wallace et al, BASL 2018
Conclusions: HEV

- Very common worldwide
- Europe: porcine zoonosis (gt3 and4)
  - Acute and chronic infection
  - Extrahepatic manifestations
  - **Neurological (~10% cases)**
    - Not jaundiced
    - Disease mechanisms and treatment: unknown
Hypothesis:
Can HEVgt3/4 cause miscarriage in humans?

• HEV gt1 pregnant women 25% maternal mortality
  • 3rd trimester, liver failure

• **HEV gt3 can cause extrahepatic damage without liver injury**

• Cause of miscarriage unknown >25%
  • unidentified virus

• HEVgt3:
  • Grows on placental cell lines; high foetal loss in infected pregnant rabbits
  • There is a lot of it about!!!