The Emerging Challenge of Hepatitis E

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Talk outline

- HEV:
  - Acute infection
  - Chronic infection

- Places HEV hides:
  - In the history books
  - In populations
  - At patient level
  - Diagnostic algorithms

- Clinical phenotype of HEV is still emerging

HEV

- RNA virus
- Genotypes 1 & 2: human disease only

- Genotype 3 (& 4):
  - Human disease
  - Found in animals (asymptomatic)
    - Pigs
      - Worldwide
    - Boar, deer, rabbits
    - Rats, ferrets, bats, cut-throat trout, mongoose

HEV in developing countries

- Major health issue
- Large outbreaks
- Genotypes 1 & 2
- Faeco-oral route via infected water
- Affects young adults
- Mortality in pregnant women 25%

HEV in developing countries: global burden of disease

- 9/21 Global Burden Disease regions:
  - 20 million infections/year
  - 70,000 deaths & 3,000 stillbirths/year

- 1,000 maternal deaths/yr in Bangladesh

HEV: in chronic liver disease

Rein et al. Hepatology 2012

Labrique et al. EID 2012

Kumar Acharya et al. J Hepatol 2007
HEV in developed countries: received wisdom

- A bit like HAV
  - Acute illness
  - Self-limiting
- Mainly seen in travellers
- Very rare in non-travellers
- Of little relevance in developed countries

Cornwall

- Good location to do epidemiological studies
- <0.5% immigrants

Jaundice hotline clinic: 1998-2014
(n > 2,600)

Acute viral hepatitis in Cornwall, UK

1. Acute HEV
2. Seronegative hepatitis
3. EBV hepatitis
4. Acute HBV
5. HAV
6. Acute HCV

Acute HEV3: Cornish experience

- 122 cases of HEV in non-travellers
  - Genotype 3
  - M:F = 3:1
  - Median age 63.5 years (range 32-92)

Acute HEV3: symptoms

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

LESS COMMON
- Pruritis
- Weight loss
- Headaches
- Arthralgia
- Neurological (n=9)
- No symptoms
Acute HEV3: Spectrum of severity

- Asymptomatic – mild hepatitis – liver failure
- Most recover 4-6 weeks
- High mortality in patients with pre-existing chronic liver disease:
  - 27% in Anglo/French study (n=372)
  - No clinical or laboratory clues to diagnosis
  - Varies by geographical location
  - Blasco-Perrin et al, submitted

HEV: Other developed countries

- USA
  - Drobenuic EID 2013
- Japan
  - Miuzo ClinMicro 2002
- Netherlands
  - Widdowson JMedVirol 2004
- Spain
  - But JVirolMethods 1995
- Italy
  - Romano J Hepat 2010
- New Zealand
  - Dalton JGastHepat 2007
- Denmark, Germany, Hungary, Sweden
  - 2009

HEV: demographics and outcome

<table>
<thead>
<tr>
<th></th>
<th>UK</th>
<th>France</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>40</td>
<td>23</td>
<td>46</td>
</tr>
<tr>
<td>Mean age</td>
<td>65 yrs</td>
<td>54.4 yrs</td>
<td>59.6 yrs</td>
</tr>
<tr>
<td>% males</td>
<td>77.5%</td>
<td>73.9%</td>
<td>87%</td>
</tr>
<tr>
<td>Deaths</td>
<td>7.5%</td>
<td>8.7%</td>
<td>10.8%</td>
</tr>
<tr>
<td>Liver deaths</td>
<td>5%</td>
<td>8.7%</td>
<td>10.8%</td>
</tr>
</tbody>
</table>

HEV3: host risk factors

- Age & male sex
- Alcohol consumption >22 units/week
- ? Diabetes
  - Is subclinical hepatic steatosis/fibrosis the key factor?
  - Dalton et al EJGH 2012

HEV3: incidence

- UK: 0.2% - 100,000 infections per year
  - Ijaz et al JID 2014
- USA: 0.7%
  - Faramwi et al EpiInf2011
- Netherlands: 1.1%
  - Slot et al Eurosurv 2013
- SW France: 3.2%
  - Abravenal et al JID 2014

HEV 3: Asymptomatic infection

- Asymptomatic infection probably very common
  - Aurora outbreak 2008
    - 33 cases hepatitis E
    - 87% asymptomatic
Re-infection with HEV

- **Genotype 4, China:**
  - 20% are re-infections
  - More common in females
  - Milder hepatitis than primary infection
  - IgM negative, IgG and PCR positive
  - Kamar et al Lancet 2012

- **Genotype 3, Toulouse, France:**
  - Reinfections quite common
  - IgG <7 WHO units/ml
  - Abravanel et al JID 2014

**HEV3: Source and route of infection**
Kamar et al Lancet Inf Dis 2008

**Acute HEV: Summary**

- Older males, Genotype 3
- Porcine zoonosis, route of infection uncertain
- Range of severity
- High incidence of infection
  - Asymptomatic infection is common
- Prognosis poor in chronic liver disease

**Chronic HEV infection: Transplant recipients**
Kamar et al NEJM 2008

- Chronic HEV3 infection in transplant patients
  - No symptoms, anicteric, ALT 200-300IU/L
- Chronicity occurs in 60% of HEV3 infections, Genotype 3 only
  - Cirrhosis
  - Low platelet count
  - Kamar et al Gastroenterology 2011
- Cirrhosis rapidly progressive
- Prevalence of chronic HEV
  - High in French transplant centre
  - Other European transplant centres: 1-4%
  - Kamar et al Transplant 2010, Pas et al EID 2012

**Chronic HEV infection: Haematological malignancy**
Tavitian et al JCV 2010

- 6 cases in Toulouse:
  - 3 acute, 3 chronic

- Allogeneic stem cell transplants, Netherlands:
  - 8 cases, 5 chronic HEV
  - 4 died with HEV viraemia
  - Versluis et al Blood 2013
  - Halac et al Gut 2012
HEV & HIV co-infection

- Small number of chronic cases:
  - HEV genotype 3
  - CD4 counts <250

HEV treatment and prevention

- Acute HEV
  - No treatment required, ribavirin in severe cases

- Chronic HEV
  - Wait (3 months)
  - Reduce immunosuppression
  - Ribavirin monotherapy
    - Longer if stool still PCR +ve

- HEV vaccine

Places HEV hides:

- Asymptomatic infection

Places HEV hides (1) history books

- HEV as an emerging disease
- HEV as an ancient disease:
  - Diverged into 4 genotypes 16th Century
  - 19th Century HEV1 common in Europe
  - HEV1 moved east (Asia) and south (Africa)
  - HEV3 hid in pigs, only recently recognised

Places HEV hides (2) at population level

- Invasive IgG assays

HEV IgG seroprevalence in developed countries
HEV IgG seroprevalence in developed countries

Wantai vs Genelabs HEV IgG assay

- PCR proven HEV3 cases (n=18)
- Serial samples n=50 (up to 7 years)
- Genelabs underestimates true seroprevalence by a factor of 4
  - Toulouse study showed seroprev of 16% using Genelabs

52%!!!!!!!

- Seroprevalence in children aged 2-4 years = 2%
  - Mansuy et al Emerg Inf Dis 2011
- Observed incidence of HEV infection in Toulouse = 3.2%
  - Mansuy et al Emerg Inf Dis 2011

Places HEV hides (3)
- patient level
HEV and blood donors

<table>
<thead>
<tr>
<th>Country</th>
<th>Blood donors</th>
<th>HEV RNA positive</th>
<th>HEV IgG seroprevalence</th>
<th>Assay</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>1:1595</td>
<td>15%</td>
<td>52%</td>
<td>Wantai, 2014; Mansuy, 2011; Mansuy, 2008</td>
<td></td>
</tr>
<tr>
<td>Midi-Pyrénées</td>
<td>1:1595</td>
<td>15%</td>
<td>52%</td>
<td>Wantai, 2014; Mansuy, 2011; Mansuy, 2008</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>1:1200</td>
<td>4.5%</td>
<td>29.5%</td>
<td>Wantai, 2014; Mansuy, 2011; Mansuy, 2008</td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>1:1781</td>
<td>27.0%</td>
<td>1.1%</td>
<td>Wantai, 2014; Mansuy, 2011; Mansuy, 2008</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>1:7986</td>
<td>21.5%</td>
<td>9.2%</td>
<td>Wantai, 2014; Mansuy, 2011; Mansuy, 2008</td>
<td></td>
</tr>
<tr>
<td>England</td>
<td>1:2848</td>
<td>12.0%</td>
<td>5.3%</td>
<td>Wantai, 2014; Mansuy, 2011; Mansuy, 2008</td>
<td></td>
</tr>
<tr>
<td>Scotland</td>
<td>1:14520</td>
<td>4.7%</td>
<td>4.7%</td>
<td>Wantai, 2014; Mansuy, 2011; Mansuy, 2008</td>
<td></td>
</tr>
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HEV and blood donors: SE England (2012-13)

- 225,000 donors
- 79 HEV RNA +ve
  - 1 in 2,848
- 60 recipients given HEV-contaminated products
- Follow-up: n=43

Recipients of blood components

<table>
<thead>
<tr>
<th>Recipient Components</th>
<th>Infected</th>
<th>Uninfected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells</td>
<td>4 (25%)</td>
<td>12 (75%)</td>
</tr>
<tr>
<td>Pooled platelets</td>
<td>4 (40%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Apheresis platelets</td>
<td>7 (50%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>2 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Pooled granulocytes</td>
<td>1 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>18 (42%)</td>
<td>25 (58%)</td>
</tr>
</tbody>
</table>

HEV and blood donors: SE England (2012-13)

- Transmission
  - More likely with high viral load in donor (p<0.0001)
  - Less likely if donor has anti-HEV antibodies
- Immunocompetent recipients (n=8)
  - Spontaneous viral clearance in all
  - Symptomatic hepatitis (n=1)
- Immunocompromised recipients
  - Asymptomatic, later infection/seroconversion
    - PCR +ve > 3 months p0?
  - 4 deaths (2 sepsis, 1 cardiac, 1 no info)

HEV and blood donors: SE England (2012-13)

- On a clinical basis alone, the resulting minimal burden of disease does not signal a pressing need for donation screening at this time

HEV and blood donors: SE England (2012-13)

- Dutch blood donors 2014
  - 1:600 are HEV RNA +ve
- Increased incidence in England
  - HEV RNA similar to European pigs
- Changes in EU food chain?
  - Processed ham and pig serum
  - Role of Food Standards Agency (UK)

Places HEV hides: with the transplant physician

- Chronic infection
  - Asymptomatic
  - ALT 100-300

Something is happening!!!
Drugs-induced liver injury (DILI)

- 3% of patients with DILI have HEV3
  - Dalto et al. APTherap 2007
- USA: 3% of DILI is HEV3 infection
  - Davern et al. Gastroenterol 2011
- Diagnosis of DILI not secure without testing for HEV

Monoclonal gammopathy of uncertain significance (MGUS)

- Occurs in 3% of the elderly
- Some develop malignancy (lymphoma, leukaemia)
- MGUS and HEV
  - 25% of patients with acute HEV3 have MGUS at presentation
  - 0% of patients with HAV, HBV, EBV have MGUS
- 2 patients with HEV3 a haematological malignancy
- Is HEV oncogenic?

HEV associated neurological syndromes:

- Guillain-Barré Syndrome
  - Bilateral brachial neuritis
  - Encephalitis, Bell’s Palsy, acute/proximal myopathy, etc
- LFTs only mildly abnormal and most cases anicteric
  - Occurs in:
    - acute and chronic HEV
    - Developed and developing countries
  - Outcome:
    - Most recover, some do not

Post infectious immune-mediated polyradiculopathy

- Infectious triggers:
  - Campylobacter: 35%
  - Unknown: 50%
- 30% abnormal LFTs? Cause

30% of GBS have abnormal LFT’s

- Are the other 25% caused by re-infection with HEV?
- Does it occur in other locations?
- Developed/developing countries
- What are the pathogenic mechanisms?
- Role of HEV in other neurological syndromes?
Places HEV hides:
Brachial neuritis

- 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 LFT's: ALT 100-300, normal bilirubin
  - 4 PCR positive: HEV genotype 3

Van Eijk et al, Neurology 2014

Places HEV hides (4):
Diagnostic algorithms

Raised ALT: differential diagnosis
1. Drug-induced hepatitis
2. Autoimmune hepatitis
3. HEV
4. EBV
5. Acute HBV
6. HAV


Current diagnostic algorithm: Raised ALT
- Check HAV, HBV and HCV
- If above are negative maybe think about HEV

Suggested diagnostic algorithm: Raised ALT
- Check HEV
- If above are negative maybe think about HAV, HBV and HCV

Conclusions: HEV in developed countries
- Common
  - HEV likes to hide
  - Porcine zoonosis
  - Significant morbidity & mortality
    - Acute and chronic
    - Progression to chronic liver disease
    - Neurological injury
  - Current diagnostic algorithms are nonsense
- Clinic phenotype of HEV is still emerging
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