Talk outline

• HEV:
  • Acute & chronic infection

• Places HEV hides:
  • History books
  • Population level
  • Patient level

• Speculation:
  • Pork Consumption and liver deaths
HEV

- RNA virus
- Genotypes 1 & 2: human disease only
  - waterborne
- Genotype 3 (& 4):
  - Human disease
  - Found in animals (asymptomatic)
    - Pigs
      - Worldwide
      - 85% UK pigs affected
    - 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 chronic liver disease

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
- v. rare in non-travellers
- Of little relevance in developed countries
HEV in developed countries: received wisdom

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

- Good location to do epidemiological studies
- <0.5% immigrants
Jaundice hotline clinic: 1998-2013 (n > 2,300)

Diagnoses in over 60's

- CBD stones
- Pancreatic/biliary cancer
- Decompensated chronic liver disease/alcohol
- Metastatic cancer
- Drug-induced liver injury
- Miscellaneous
- Unknown
Acute HEV3: clinical features

- 73 cases of HEV in non-travellers
  - 58/73 HEV PCR +ve, all genotype 3
- M:F = 3:1
- Median age 63.5 years (range 32-92)

Dalton et al J Viral Hepatitis 2007
Dalton et al Eur J Gastro 2008
Vine et al APT 2012
Acute HEV3: symptoms

- Jaundice (n=44)
- Anorexia (n=27)
- Lethargy (n=27)
- Abdo pain (n=25)
- Vomiting (n=12)
- Fever (n=12)
- Myalgia (n=11)
- Pruritis (n=10)
- Weight loss (n=7)
- Headaches (n=6)
- Arthralgia (n=6)
- Neurological (n=7)
- No symptoms (n=3)
Acute HEV3: Spectrum of severity

• Asymptomatic – mild hepatitis – liver failure
• Most recover 4-6 weeks
• 70% mortality in patients with pre-existing chronic liver disease

*Dalton et al Lancet 2007
Peron et al JViralHepat 2007*
## HEV: Other developed countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>Halbur <em>JClinMicro</em> 2001</td>
</tr>
<tr>
<td>Japan</td>
<td>Miuzo <em>ClinMicro</em> 2002</td>
</tr>
<tr>
<td>France</td>
<td>Mansuy <em>JMedVirol</em> 2004</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Widdowson <em>JMedVirol</em> 2004</td>
</tr>
<tr>
<td>Spain</td>
<td>Buti <em>JVirolMethods</em> 1995</td>
</tr>
<tr>
<td>Italy</td>
<td>Romano <em>J Hepatol</em> 2010</td>
</tr>
<tr>
<td>New Zealand</td>
<td>Dalton <em>JGastHepatol</em> 2007</td>
</tr>
<tr>
<td>Denmark, Germany, Hungary, Sweden</td>
<td>2009-10</td>
</tr>
</tbody>
</table>
HEV: demographics and outcome

<table>
<thead>
<tr>
<th></th>
<th>UK</th>
<th>France</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Dalton et al 2008</em></td>
<td><em>Peron et al 2006</em></td>
<td><em>Okamoto et al 2003</em></td>
</tr>
<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: incidence

- More common than HAV
  
  * Dalton et al EuroJClinMicro 2008  
  * Vine et al AlimentPharmacol Therap 2012

- Geographical variation:
  
  * UK: 0.2%
    
    * Ijaz et al 2009 JClinVirol
  
  * USA: 0.7%
    
    = > 2 million infections per year
    
    * Faramwi et al EpidInfect 2011
HEV 3: Asymptomatic infection

- Asymptomatic infection probably very common

- Aurora outbreak 2008
  - 33 cases hepatitis E
  - 67% asymptomatic

*Said et al. EmInfDis 2009*
HEV3: Source and route of infection
Chronic HEV infection: Transplant recipients

- Chronic HEV3 infection in transplant patients  
  - No symptoms, anicteric, ALT 200-300IU/L  
  
- Chronicity occurs in 60% of HEV3 infections  
  - Tacrolimus  
  - Low platelet count  

- Cirrhosis rapidly progressive  

- Very high incidence of chronic HEV in French transplant centres  

- Prevalence in other European transplant centres: 1-2%
Chronic HEV infection: HIV

- 48-yr old bisexual male, alcohol ++
- HIV-1 since 2001, SE Asia
- TB treated 2003
- Anti-retroviral therapy started 2007
  - CD4: 30 cells/mm³
  - viral load: 82649 copies/ml
- LFT’s abnormal, neurological symptoms
  - ?Drug reaction
- Chronic HEV3 infection

Dalton et al NewEngJMed 2009
HEV & HIV co-infection

• Small number of cases in Europe
  – 5 chronic HEV, 2 cirrhotic
    • CD4 counts <250
      
      *Dalton et al NewEngJMed 2009*
      *Colson et al J Viral Hepatitis 2011*
      *Foguena et al Emerg Infec Dis 2011*
      *Kaba et al J Med Virol 2011*
      *Jagjit Singh et al J Infection 2012*

• No evidence of sexual transmission

  *Keane et al 2012, HIV Med*
HEV & HIV chronic co-infection: potential burden of disease

Geographic Distribution of Hepatitis E

Outbreaks or Confirmed Infection in >25% of Sporadic Non-ABC Hepatitis
Places HEV hides:
Places HEV hides (1): history books

- HEV as an emerging disease
- Old disease
  - Diverged into 4 genotypes 18\textsuperscript{th} Century
  - 19\textsuperscript{th} Century HEV1 common in Europe
  - HEV1 moved east (Asia) and south (Africa)

\textit{Teo EpidemiolInfect 2012}

- HEV3 hid in pigs, only recently recognised
Places HEV hides (2): at population level
HEV serology

- Poor concordance between assays
- IgG assays particularly problematic
HEV IgG seroprevalence in developed countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>16%</td>
</tr>
<tr>
<td>New Zealand</td>
<td>4%</td>
</tr>
<tr>
<td>Denmark</td>
<td>20.6%</td>
</tr>
<tr>
<td>Tokyo</td>
<td>3%</td>
</tr>
<tr>
<td>8 US States</td>
<td>18.3%</td>
</tr>
<tr>
<td>Moldova</td>
<td>24.7%</td>
</tr>
<tr>
<td>Iowa</td>
<td>3.3%</td>
</tr>
<tr>
<td>New York</td>
<td>31%</td>
</tr>
<tr>
<td>California</td>
<td>13.7%</td>
</tr>
<tr>
<td>Baltimore</td>
<td>21.3%</td>
</tr>
<tr>
<td>SW France</td>
<td>16.6%</td>
</tr>
<tr>
<td>Northern France</td>
<td>3.2%</td>
</tr>
<tr>
<td>Catalonia</td>
<td>7.3%</td>
</tr>
<tr>
<td>Australia</td>
<td>0.4%</td>
</tr>
<tr>
<td>Holland</td>
<td>1%</td>
</tr>
<tr>
<td>Austria</td>
<td>3%</td>
</tr>
<tr>
<td>Greece</td>
<td>0.26%</td>
</tr>
<tr>
<td>Sweden</td>
<td>9.2%</td>
</tr>
<tr>
<td>San Marino</td>
<td>1.5%</td>
</tr>
<tr>
<td>Madrid</td>
<td>2.8%</td>
</tr>
<tr>
<td>Stockholm</td>
<td>5.2%</td>
</tr>
<tr>
<td>Calabria/Italy</td>
<td>1.7%</td>
</tr>
<tr>
<td>UK</td>
<td>5.3%</td>
</tr>
<tr>
<td>Barcelona</td>
<td>5.5%</td>
</tr>
<tr>
<td>Switzerland</td>
<td>3.2%</td>
</tr>
<tr>
<td>Italy</td>
<td>1.2%</td>
</tr>
<tr>
<td>Holland</td>
<td>1.1%</td>
</tr>
</tbody>
</table>
HEV IgG seroprevalence in developed countries

16%
Wantai vs Genelabs HEV IgG assay

Bendall et al J Med Virol 2010

- 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
HEV IgG seroprevalence in developed countries

Key
- Genelabs assay
- Wantai assay

- 52% in developed countries
- 18% in other regions
- 4% in some areas
52% !!!!!!!

- Seroprevalence in children aged 2-4 years = 2%
- Observed incidence of HEV infection in Toulouse = 3.2%

Mansuy et al Emerg Inf Dis 2011
HEV IgG seroprevalence in developed countries
Places HEV hides (3): at patient level
Places HEV hides: with the Neurologist

- HEV is neuropathogenic:
  - inflammatory polyradiculopathy
  - Guillain–Barré syndrome
  - bilateral brachial neuritis
  - Encephalitis, Bell’s Palsy, ataxia/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
Places HEV hides:
With the Hepatologist: Drug-induced liver injury (DILI)

- 13% of patients with DILI have HEV3
  
  *Dalton 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
Places HEV hides:
with the transplant physician

• Chronic infection
  • Asymptomatic
  • ALT 100-300
Places HEV hides: with the Cardiologist

- 70 year old male
- Anterior MI 15 years previously
- Presents with ventricular tacchycardia (VT)
  - Successfully cardioverted
  - ALT 1,250, bilirubin 16
  - Diagnosis: scar-VT with ischaemic hepatitis
- HEV genotype 3
Places HEV hides: blood supply
Places HEV hides:
patients with decompensated chronic liver disease

- 76 yr old male
- Alcohol 35U/week
- Decompensated +++
  - Bilirubin 86
  - ALT 2286
- Transferred to another hospital
- Died at 4 months of ‘decompensated alcoholic liver disease due to alcoholic hepatitis’
Speculation:
Pork consumption & liver deaths
Speculation: 
Pork consumption & liver deaths

• Deaths from cirrhosis vs ethanol consumption & pork consumption
• Developed countries (1965, mid 1970’s)

*Lancet 1985*
Fig 3—Relationship between cirrhosis mortality and pork consumption.
Mortality from chronic liver disease vs alcohol consumption 1990 - 2000

Dalton et al Epidemiol Infect 2010

\[ R^2 = 0.473 \quad p = 0.002 \]
Mortality from chronic liver disease vs pork consumption 1990 - 2000

$R^2 = 0.531 \quad p = 0.001$
Multiple regression:

• Independent predictors of mortality:

  • Alcohol consumption   (p=0.005)
  • HBV seroprevalence    (p=0.037)
  • Pig meat consumption  (p<0.001)
Possible explanations:

1. Epiphenomenon

2. A factor in pork causes cirrhosis

3. A factor in pork causes death in patients with pre-existing cirrhosis? HEV3

   • HEV3 found in retail pig meat
     » USA, Holland, Japan, UK & France
   • HEV survives cooking at 56°C & can be transmitted by eating infected meat
   • HEV mortality in chronic liver disease = 70%
HEV: potential mortality in developed countries

- Assuming:
  - Prevalence of chronic liver disease = 1%
  - Mortality HEV in chronic liver disease = 70%
  - Population of USA, Canada, EU, Japan, Australia & NZ = 931 million
  - Annual HEV seroconversion rate = 0.2%

- 13,000 deaths/annum attributable to HEV infection in patients with chronic liver disease
HEV in developed countries: received wisdom

- A bit like HAV
  - Acute illness
  - Self-limiting
- Mainly seen in travellers
- v. rare in non-travellers
- Of little relevance in developed countries
Conclusions:
HEV in developed countries

- Common
  - HEV likes to hide
- Zoonosis
- Significant morbidity & mortality
- Prognosis poor in chronic liver disease
- May cause up to 13,000 deaths per year
Acknowledgments

• Lemon Street Gallery, Truro
• Sheila Sherlock Travelling Bursary 2011
• Office of Chief Scientist Scotland
• Duchy Charity
research collaborators

• Colleagues in SW England:
  • **Dr Richard Bendall**
  • Dr Frances Keane (Truro), Dr Mark Gompels (Bristol)

• UK, national:
  • Malcolm Banks: Veterinary Laboratory Association (Surrey)
  • Linda Scobie: Glasgow Caledonian University, Scotland
  • Adrian Stanley: Glasgow Royal Infirmary
  • Prof Richard Tedder, Dr Samreen Ijaz: Health Protection Agency (London)
  • Ellie Barnes: University of Oxford

• International:
  • Bob Purcell/Sue Emerson, NIH, Bethesda, Maryland, USA
  • Hans Zaaijer and Bart Jacobs, The Netherlands
  • Alessandro Bartoloni, Florence, Italy
  • Prof Ting Wu, Xiamen University, China
  • **Jacques Izopet, Nassim Kamar & colleagues, Toulouse, France**
Caution: May contain HEV