HEV infection in developed countries

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Talk outline: HEV

• HEV in developed countries
  – Acute
  – Chronic
• Seroprevalence
  • Hypothesis #1
• Places HEV hides: unrecognised infection
• Speculation: Pork Consumption and liver deaths
  • Hypothesis #2
HEV in developing countries

- Major health issue
  - Large outbreaks
- 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

- RNA virus
- Genotypes 1 & 2: human disease only
- Genotype 3 (& 4):
  - Human disease
  - Found in animals (asymptomatic)
    - Pigs
      - Worldwide
      - 85% UK pigs affected
      - 20% of pig herd excrete HEV in faeces
    - Boar, deer, mongoose
- Worldwide
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

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HEV in developed countries: received wisdom

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Cornwall

- Good location to do epidemiological studies
- <0.5% immigrants
Jaundice hotline clinic: 1998-2011 (n = 2100)

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

- 62 cases of HEV in non-travellers
  - 42/62 HEV PCR +ve, all genotype 3
- M:F = 3:1
- All Caucasian
- Median age 63.5 years (range 35-86)

*Dalton et al J Viral Hepatitis 2007*
*Dalton et al EurJGastro 2008*
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)
- Paraesthesiae (n=3)
- No symptoms (n=3)
Acute HEV3: Spectrum of severity

• Asymptomatic – mild hepatitis – liver failure
• Bilirubin 120μmol/l (range 3-417)
• ALT 1465 IU/L
• 59/62 recovered (usually in 4 – 6 weeks)
• 3 patients died
Hepatic complications

• **Cornwall**
  - All had pre-existing cirrhosis
  - Self-limiting encephalopathy (n=1): survived
  - Sub-acute liver failure (n=2): died at 4 and 5 months
    *Dalton et al Lancet 2007*

• **France**
  - Poor prognosis in patients with chronic liver disease
  - 70% mortality

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

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

**References:**
- Dalton et al 2008
- Peron et al 2006
- Okamoto et al 2003
HEV3: incidence

• Uncertain

• Geographical variation:
  • UK: 0.2% (130,000 cases/year)
  • Toulouse: 3.2%

IJaz et al 2009 JClinVirol

Legrand-Abravanel et al Emerg Inf Dis 2011
### HEV vs HAV

**Devon and Cornwall 2005-6**

<table>
<thead>
<tr>
<th></th>
<th><strong>HEV</strong></th>
<th><strong>HAV</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tests</td>
<td>838</td>
<td>4503</td>
</tr>
<tr>
<td>Cases</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>Age*</td>
<td>65 (35-86)</td>
<td>41 (8-74)</td>
</tr>
<tr>
<td>M:F</td>
<td>4.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Complications</td>
<td>n=5</td>
<td>n=0</td>
</tr>
<tr>
<td>Death</td>
<td>n=2</td>
<td>n=0</td>
</tr>
</tbody>
</table>

* indicates statistical significance at p < 0.05

*Dalton et al EurJClinMicro 2008*
HEV 3: Asymptomatic infection

- Asymptomatic infection probably very common

- Aurora outbreak 2008
  - 33 cases hepatitis E
  - HEV 3: identical on sequencing
  - Foodborne outbreak
  - Source uncertain
    - ?shellfish
  - >50% asymptomatic

Said et al EmInfDis 2009
HEV: re-infection

- Does occur
- May be quite common???
- Level of protective antibody uncertain
HEV3: Source and route of infection

- Vocational exposure: vets, farmers, processing and retail staff
- Ingestion of undercooked Sika deer meat
- Ingestion of undercooked pig meat, liver
- Watercourses
- Crops via irrigation
- Water-based recreation
- Abstraction for drinking water
- Blood Transfusion
- Molluscs
- Human sewage, floods
- Run-off from outdoor pig farms
- Slurry
- Faeces
- Pig
- Abattoir Effluent
- Pasture
- Man
- Other mammals
Summary: acute HEV

• Older males, Genotype 3
• Porcine zoonosis, route of infection uncertain
• Range of severity and complications
• High incidence of infection
• Prognosis poor in chronic liver disease
Chronic HEV infection in the immunosuppressed
Chronic HEV infection: Transplant recipients

- Chronic HEV3 infection in transplant patients
  

- Chronicity occurs in 60% of HEV3 infections
  - Tacrolimus
  - Low platelet count

  Kamar et al Gastroenterology 2011

- Cirrhosis rapidly progressive

  Kamar et al Transplantation 2010

- Very high incidence of chronic HEV in French transplant centres
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

- Spain
  - 93 HIV patients, 43 with abnormal LFTs
  - All HEV PCR –ve
    
    Madejon et al. JViralHep 2009

- France:
  - 108 HIV patient with abnormal LFTs
  - No cases of chronic HEV infection
    
    Sellier et al. Virology J 2011

- UK:
  - 138 unselected HIV cases
  - No cases of chronic HEV infection
  - No evidence of sexual transmission of HEV
    
    Keane et al. 2011, HIVmed 2011
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
HEV: Treatment

• **Acute HEV**
  - No treatment required in most cases
  - Ribavirin monotherapy in patients with chronic liver disease
    *Peron et al J Hepatol 2011*

• **Chronic HEV**
  - Transplant patients:
    - Reduce immunosuppression
    - $\alpha$-interferon monotherapy
      *Kamar et al ClinInfDis 2010*
    - Ribavirin monotherapy
      *Kamar Gastroenterol 2010*
  - HIV patient:
    - $\alpha$-interferon and ribavirin
HEV: prevention

• Chinese HEV vaccine is effective & safe
  *Lancet 2010*

• Not yet licensed for use
HEV IgG seroprevalence in developed countries
HEV IgG seroprevalence in developed countries

- Wide range of results:
  - Demographics of population studied
  - True differences in seroprevalence
  - Differing assays used
HEV IgG seroprevalence
16% : blood donors SW England

Dalton et al EuroJGastroHep 2008
HEV IgG seroprevalence in developed countries

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

- 0.4%
- 4%
- 3%
- 7.3%
- 13.7%
- 16%
- 18.3%
- 20%
- 21%
- 25%
- 31%
- 33%
HEV IgG seroprevalence in developed countries

Key:
- Genelabs assay
- Wantai assay
- In house assay

HEV IgG seroprevalence

- Gene Labs assay: 0.4%
- Wantai assay: 4%
- In house assay: 31%
HEV IgG seroprevalence in developed countries

Key
- Genelabs assay
- Wantai assay

- 16%
- 4%
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)
  • Wantai +ve 98%
  • Genelabs +ve 50%
    » High negative seroconversion rate after 12 months
• Genelabs cut off 10X higher than Wantai
  » Genelabs = 2.5 WHO units
  » Wantai = 0.25 WHO units
• HEV IgG seroprevalence in UK blood donors (n=500)
  • Wantai = 16.2%
  • Genelabs = 3.6%
• Genelabs underestimates true seroprevalence by a factor of 4
<table>
<thead>
<tr>
<th></th>
<th>SW England</th>
<th></th>
<th>SW France</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Blood donors</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Anti-HEV</td>
<td>16%</td>
<td></td>
<td>16%</td>
</tr>
<tr>
<td>seroprevalence</td>
<td></td>
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<tr>
<td>Assay used</td>
<td>Wantai</td>
<td></td>
<td>Genelabs</td>
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</table>
Hypothesis #1:
HEV may be hyper-endemic in SW France
Hypothesis #1: HEV may be hyper-endemic in SW France

- Observed incidence in Toulouse transplant population = 3.2%

- Molecular techniques used

Legrand-Abravanel et al Emerg Inf Dis 2011
HEV IgG seroprevalence in developed countries

Map Country Key
- UK 16%
- New Zealand 4%
- Denmark 20.6%
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- 8 US States 18.3%
- Moldova 24.7%
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- Calabria/Italy 1.7%
- UK 5.3%
- Barcelona 5.5%
- Switzerland 3.2%
- Italy 1.2%
- Holland 1.1%
HEV IgG seroprevalence in developed countries
Places HEV hides
HEV Seroprevalence UK: 16% why so high???

- ? Inaccurate HEV IgG assay
  - validated against HEV3 convalescent sera
    
    *Bendall et al JClVirol 2010*

- ? Sub-clinical infection
  - >50% of HEV infections are asymptomatic (Aurora outbreak)
    
    *Said et al EmInfDis 2009*

- ? Unrecognised infection
  - HEV hides in unusual places…..
Unrecognised infection (1): Drug-induced liver injury (DILI)

- 13% of patients with DILI have HEV
- Diagnosis of DILI not secure without testing for HEV

» Dalton et al
  APharmTherap
  2007
Unrecognised infection (2): HEV neuropathy

Kamar et al Emerg Inf Dis 2011

- Occurs in about 5% of cases (acute & chronic)
- LFTs only mildly abnormal
  - Inflammatory polyradiculopathy (n=6)
    • Complete resolution (n=4), Partial improvement (n=2)
  - Encephalitis (n=1)
    • Patient died
- HEV isolated from CSF (n=4)
  • CSF viral clearance coincides with symptom improvement
- Other neurological syndromes: ? Guillian Barre Syndrome
Unrecognised infection (3):

- 72 year old male
- Vomiting ++++
- ALT 600
- Ruptured oesophagus
  - Surgical repair
  - Intensive Care for 2 months

Kurt Jackson 2007
Unrecognised infection (4): in chronic liver disease

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

Diet and Disease

RELATIONSHIP BETWEEN PORK CONSUMPTION AND CIRRHOSIS

AMIN A. NANJI  SAMUEL W. FRENCH

Department of Pathology, University of Ottawa and Ottawa General Hospital, Ottawa, Ontario, Canada

- Deaths from cirrhosis vs ethanol consumption & pork consumption
  - Developed countries (1965, mid 1970’s)
  - Provinces of Canada (1978)

*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

R²=0.473  p=0.002
Mortality from chronic liver disease vs pork consumption 1990 - 2000

R²=0.531   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
     
     Colson et al. JID 2010

   - HEV survives cooking at 56°C & can be transmitted by eating infected meat
   - HEV mortality in chronic liver disease = 70%
Hypothesis #2
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
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- Mainly seen in travellers
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- Of little relevance in developed countries
Conclusions: HEV in developed countries

- Commonest cause of acute viral hepatitis
- ?hyper-endemic SW France
- Probably porcine zoonosis
- Significant morbidity & mortality
- Prognosis poor in chronic liver disease
- May cause up to 13,000 deaths per year
- Burden of chronic infection unknown
Acknowledgments

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• Duchy Charity
• Royal College of Physicians, London

Sheila Sherlock Travelling Bursary 2009, 2011
research collaborators

• Colleagues in SW England:
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  • 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
  • Dan Webster: University of Brighton
  • Scottish Liver Transplant Centre, Edinburgh

• International:
  • Bob Purcell/Sue Emerson, NIH, Bethesda, Maryland, USA
  • Centres for Disease Control (CDC), Atlanta, Georgia
  • Prof Ting Wu, Xiamen University, China
  • Jacques Izopet & colleagues, Toulouse, France
HEV Viral Load (GEq/ml)

- HEV plasma VL
- HEV stool VL
- CD4
- ALT

ALT (IU/L) and CD4 count (cells/mm$^3$)

- 135µg/week Peg α-interferon
- 135µg/week Peg α-interferon + 1000mg/day Ribavirin
- 135µg/week Peg α-interferon + 500mg/day Ribavirin
HEV plasma VL
HEV stool VL
CD4
ALT

1.0E+07
1.0E+08

300

1.0E+05
1.0E+06

200

200
100

1.0E+03
1.0E+04

1.0E+00

0

ALT (IU/L) and CD count (cells/mm²)

July-07
Aug-07
Sept-07
Dec-08
Jan-09
Feb-09
Mar-09
Apr-09
May-09
Jun-09
Jul-09
Aug-09
Sept-09
Oct-09
Nov-09
Dec-09
Jan-10
Feb-10
Mar-10
Apr-10
May-10
Jun-10
Jul-10
Aug-10
Sept-10
Oct-10
Nov-10
Dec-10
Jan-11

135µg/week Peg α-interferon
135µg/week Peg α-interferon + 1000mg/day Ribavirin
135µg/week Peg α-interferon + 500mg/day Ribavirin

HEV Viral Load (GEq/ml)

CD4

ALT (IU/L) and CD count (cells/mm²)