Hepatitis E Virus and neurological injury: has HEV been misnamed?

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HEV worldwide

- 1st cause of acute hepatitis

- 20 million infections per year,
  - Over 3 million symptomatic cases,
  - 56 600 hepatitis E related deaths

- New Delhi 1955-56 epidemic: 29 000 symptomatic cases

Lozano R Lancet 2012
Indian J Med Res 1957
HEV diversity

7 genotypes (4 main genotypes)
- genotypes 3 and 4, 7 : zoonosis

1 serotype
Worldwide distribution

Human HEV
Geographic Distribution of Genotypes

Genotype: 1  2  3  4
## Comparison of HEV genotypes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HEV 1 and 2</th>
<th>HEV3 and 4</th>
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<tbody>
<tr>
<td><strong>Source of infection</strong></td>
<td>Obligate human pathogen</td>
<td>Zoonotic Blood supply</td>
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<tr>
<td><strong>Route of infection</strong></td>
<td>Faecal-oral via infected water</td>
<td>Consumption of infected pork Blood supply</td>
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<tr>
<td><strong>Outbreaks</strong></td>
<td>Yes</td>
<td>No</td>
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<tr>
<td><strong>Clinical attack rate</strong></td>
<td>1:5</td>
<td>&lt; 1:10</td>
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<tr>
<td><strong>Demographics</strong></td>
<td>Mainly affects young adults</td>
<td>Mainly affects older men Male:female ratio 3:1</td>
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<tr>
<td><strong>Chronic infection</strong></td>
<td>No</td>
<td>Yes in immunosuppressed individuals</td>
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<tr>
<td><strong>Occurrence of second HEV infection</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Neurological sequelae</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Seroprevalence

Stramer SL Transfusion 2015
Izopet J Clin Virol 2015
Dalton H Curr Infect Dis Rep 2014
IgG and IgM seroprevalence in French blood donor

Blue < 10%, green 20-30%, yellow 30-40%, pink 40-50%
Orange 60-70%, brown > 70%

Mansuy et al Hepatology 2016
Adult

Incubation: 40 days

- No symptoms > 95%
- Clinical symptoms: < 95%
  - Prodromic phase 3 to 7 days
  - Jaundice phase 1 to 2 weeks

Severe or fulminant hepatitis
- 0.5 to 4% mortality
  - Elderly patient
  - Cirrhosis
  - Neurological symptoms

No chronic hepatitis
- In immunocompetent patients
contamination

HEV in stools

HEV in the liver

HEV in the blood

ALT

Anti-HEV IgG

anti-HEV IgM

weeks
HEV in stools

HEV in the liver

HEV in the blood

contamination

ALT

Anti-HEV IgG

anti-HEV IgM
Neurological disorders during HEV infection

30 patients
All but 1 European
HEV3

36 patients
HEV1 and HEV3

Worldwide cases
Probably pangenotypic

Mild liver symptoms or injury

Neurological disorders during HEV infection

- 126 patients with locally acquired acute or chronic hepatitis HEV3 infection
- 2 hospitals (Toulouse, Truro UK), 2004-2009

- Neurological symptoms: 5.5%
  - Inflammatory polyradiculopathy (n=3)
  - Guillain Barré syndrome (n=1)
  - Bilateral brachial neuritis (n=1)
  - Encephalitis (n=1)
  - Ataxia/proximal myopathy (n=1)
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Kamar N Emerg Infect Dis 2011
Quasi-species: HEV compartmentalization between cerebrospinal fluid and serum and temporal association

Serum obtained after 12 months and 33 months, cerebrospinal fluid after 33 months

Kamar N et al Am J Gastroenterol 2010
Neurological disorders during HEV infection

• French retrospective study,
• Immunocompetent patients, 2006-2013
• Wide range of neurological disorders

• 14 patients (11 HEV PCR pos, all genotype 3 f)
• 4 main entities
  – Mononeuritis multiplex (n= 6)
    • asymmetric, asynchronous involvement of the noncontiguous nerve trunks
  – Neuralgic amyotrophy (Parsonage Turner syndrome) (n=4)
    • acute neuropathic pain in the shoulder bilateral but asymmetric in 3 patients
  – Meningoradiculatis (n=3)
  – Acute demyelinating neuropathy (GBS) (n=2)

Perrin et al. EID 2015
Neurological disorders during HEV infection: risk of sequelae

- Mononeuritis multiplex (n=6): 1 patient had sequelae consisting of ongoing paresthesia

- Neuralgic amyotrophy (Parsonage Turner syndrome) (n=4): 3 had sequelae consisting of persistent weakness

- Meningoradiculatis (n=3): no sequelae

- Acute demyelinating neuropathy (GBS) (n=2), sequelae in 1 consisting of persistent ataxia

Perrin et al. EID 2015
Neurological amyotrophy during HEV infection: a particular phenotype?

- Neuralgic amyotrophy (Parsonage Turner syndrome)
  - Grenoble University Hospital
  - Retrospective case series
  - 5 cases
  - Particular phenotype of neuralgic amyotrophy associated with HEV
    - Bilateral
    - Asymmetric
    - Involvement of nerves outside the brachial plexus

Physiopathology of neurological disorders during HEV infection

- **Immunomodulated mechanism:**
  - Neuralgic amyotrophy (PTS)
  - Guillain Barré
  - Persisting symptoms, sequelae+++

- **Direct mechanism**
  - Mononeuritis multiplex
  - Meningitis
  - No sequelae
Physiopathology of neurological disorders during HEV infection

• Extrahepatic replication and infection of HEV in neuronal-derived cells
  – Neuroepithelioma
  – Desmoplastic cerebellar medulloblastoma
  – Glioblastoma multiforme
  – Glioblastoma astrocytoma
  – Oligodendrocytic cells

• All tested cell lines supported HEV RNA replication

• Extra and intracellular viral capsid detected

• HEV tropism is not restricted to the liver and HEV can potentially complete the full viral cycle in neuronal-derived tissues

Drave SA et al J viral Hepat 2016
Prevalence of HEV infection in patients with neurological symptoms: neuralgic amyotrophy

- Neuralgic amyotrophy (Parsonage Turner syndrome)
  - Royal Cornwall hospital UK, Radboud University Nijmegen MC, Netherlands
  - Retrospective and prospective cohorts

- 10%: 5/47 patients (4 HEV PCR pos)
  - Bilateral brachial involvement (1/2 in non HEV cases)
  - Significant residual neurologic impairment at 6 months

Van Eijk JJ Neurology 2014
Prevalence of HEV infection in patients with neurological symptoms: Guillain Barré syndrome

- Guillain Barré syndrome
  - Royal Cornwall hospital UK, Radboud University Nijmegen MC, Netherlands
  - 201 patients with GBS, 201 healthy controls
  - 5%: 10/201 patients (Pos PCR in 4 patients), mildly increased liver tests in 70%
    - (1/201 in the healthy controls, OR 10.5, 95% confidence interval 1.3-82.6, p = 0.026)

Van den Berg B Neurology 2014
Prevalence of neurological disorders during HEV infection

- Monocentric study Southwest France
  - 61 consecutive immunocompetent patients
  - Jan 2012 – July 2016
  - Toulouse University Hospital
  - Mean age 52 years old
  - 19 % neurological disorders

- French cohort of all diagnosed cases of HEV infection in France
  - 200 consecutive patients,
  - French National Reference Center for HEV
  - Prospective study, systematic telephone interview
  - Jan 2015-Jan 2016
  - 18 % neurological disorders

Unpublished data Mogno J and Pique j
Conclusion

1. HEV is associated with a range of subacute monophasic neurological injuries, in particular Guillain Barré syndrome, neuralgic amyotrophy, encephalitis/myelitis and mononeuritis.

2. In patients with HEV-associated neurological injury, the neurological features dominate the clinical picture and hepatitis is either mild or absent.

3. Prevalence of neurological symptoms in patients with acute hepatitis E can reach 20% (prevalence in patients infected with HEV?)

1. Mechanism may be immunomediated or direct depending on the neurological injury.
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