Extra-hepatic HEV

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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 developed countries

Porcine zoonosis

- Consumption infected pork meat

Acute hepatitis

- Older males

Chronic hepatitis

- Immunosuppressed
- Rapidly progressive cirrhosis

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HEV in developed countries

Porcine zoonosis

- Consumption infected pork meat

Acute hepatitis

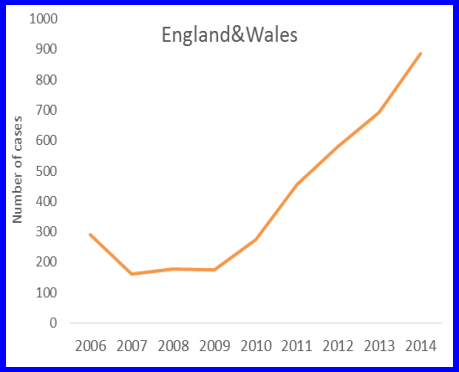
- Older males

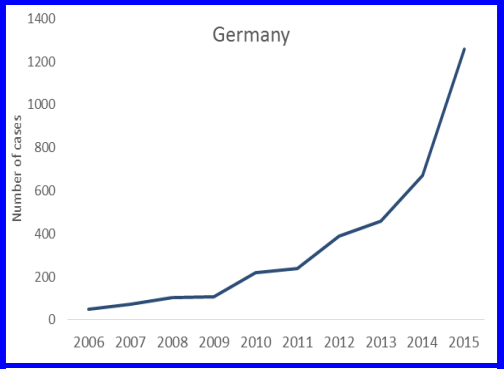
Chronic hepatitis

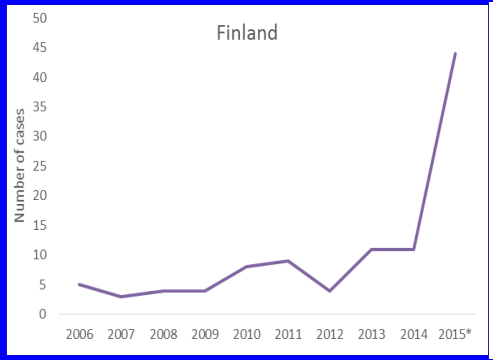
- Immunosuppressed
- Rapidly progressive cirrhosis

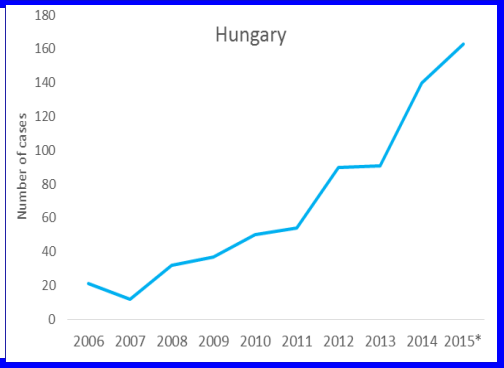
Common

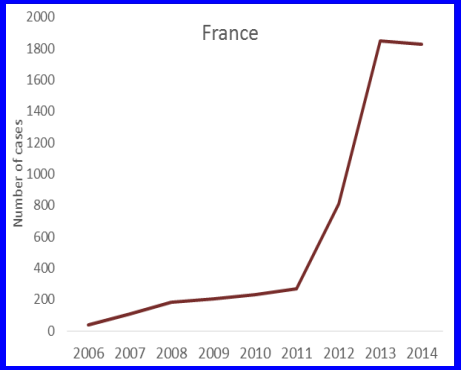
- Incidence increasing

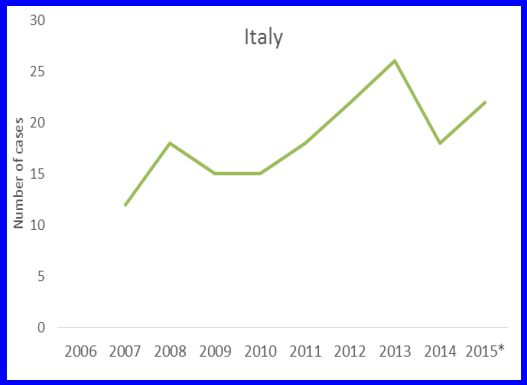










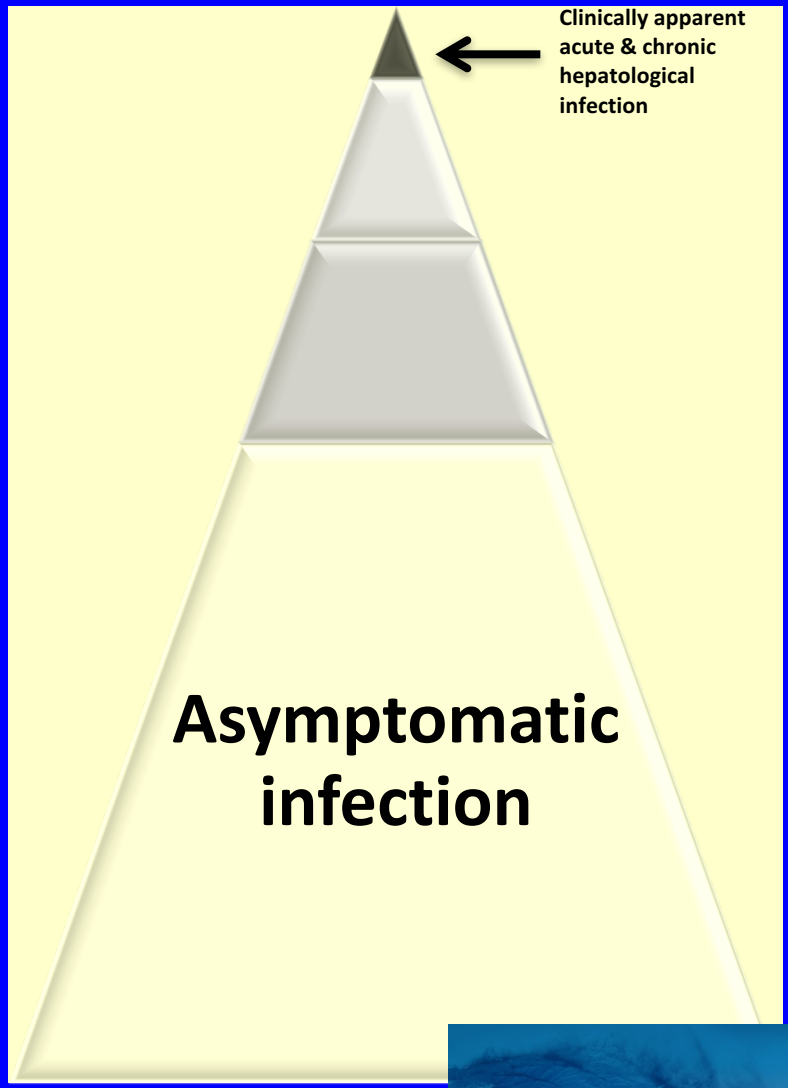


HEV3: incidence

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

  100,000 infections per year
- USA: 0.7% *Faramwi et al EpiInf2011*
- 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



Hewitt et al Lancet 2014, Tedder et al Transfusion 2016

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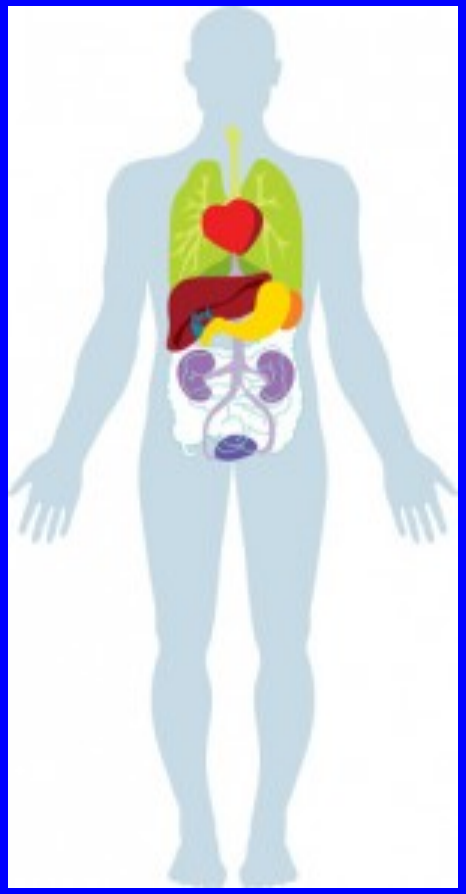
Extra-hepatic manifestations of HEV

- Case reports
- Case series
- Controlled studies



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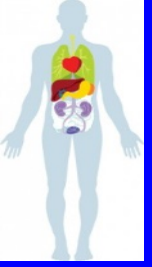
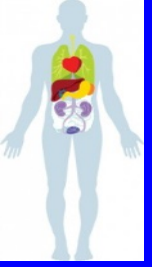
"Association does not necessarily imply causation……"

An anonymous referee, New England Journal of Medicine



HEV: extra-hepatic manifestations

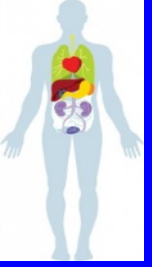
- Case reports
  - Autoimmune thyroiditis
  - Myocarditis
  - Cryoglubinaemia
  - Bell's palsy



HEV and myocarditis

- Cornwall case
  - 73 year old male
  - Ventricular tachycardia, ALT > 1,000, ?ischaemic hepatitis
  - Acute HEV, PCR -ve
- Cases form India
  - 3 young men from India
  - Acute hepatitis E (basis for diagnosis?)
  - Decreased LV function on echo
  - 1 died

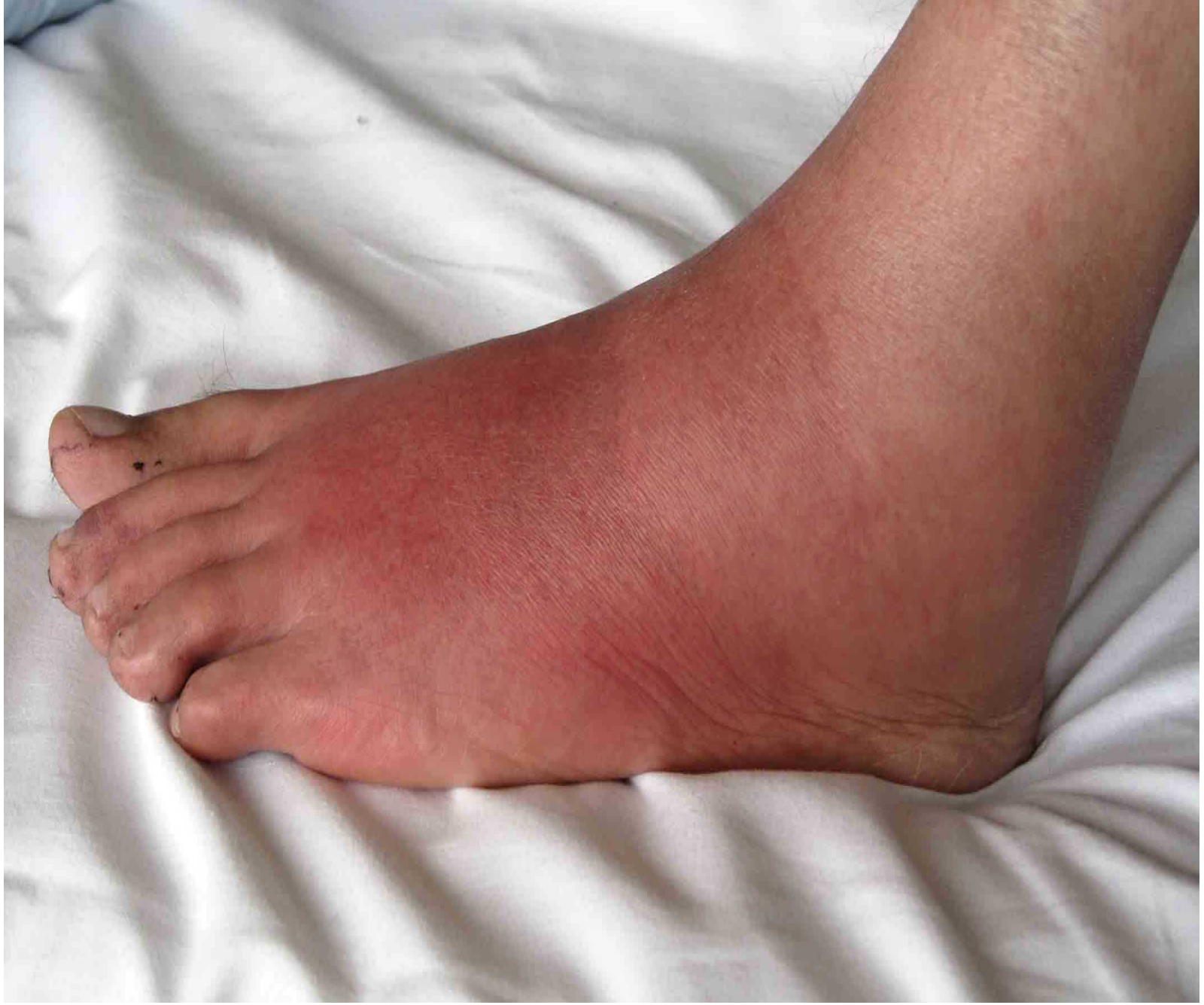
Wooslon et al AP&T 2015, Premkumar et al Case Rep Hepatol 2105



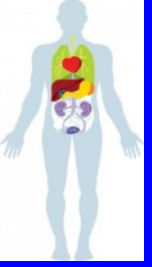
HEV & Cryoglubuilameia

- 35 yr old male liver transplant patient
- Chronic HEV > 2years
- Acute on chronic kidney failure
- Myalgia, arthralgia
    - Raised creatine kinase
- Rash lower limbs

Pischke et al. Lancet Infectious Diseases 2014



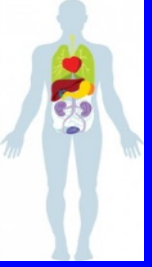
Pischke et al. *Lancet Infectious Diseases 2014*



HEV & Cryoglubuilameia

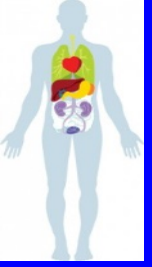
- Type 3 cryoglobulins
- Treatment:
  - Steroids
  - Increased immunospression
  - Rash disappeared, renal function normal
- Steroids tapered
  - Rash and cryoglobs re-appeared
  - Thrombocytopenia
  - Fatal GI bleed

Pischke et al. Lancet Infectious Diseases 2014



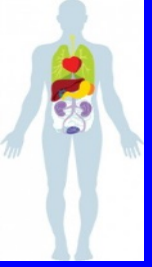
HEV: extra-hepatic manifestations Case series

- Pancreatitis
- Thrombocytopenia
- Monoclonal gammopathy
- Renal disease
- Neurological syndromes



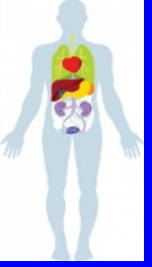
HEV and acute pancreatitis

- 13 case reports, 4 case series
- 55 patients all from S Asia
  - Mean age 28 years
  - M:F = 18:1
- Severe pancreatitis 18%
- 2 deaths (3.6%)
- No studies with HEV genotypes 3 and 4



HEV and Thrombocytopenia

- Occurs in 11.3% (acute HEV3)
- Rarely severe
  - 3% have platelet count <100 *Woolson et al AP&T 2014*
  - Occasionally life-threatening *Colson et al JClin Micro 2008*



HEV and MGUS

- Monoclonal gammopathy of uncertain significance (MGUS)
  - Occurs in 1% of the elderly
  - Some develop malignancy (myeloma, 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 » haematological malignancy
- Is HEV oncogenic?

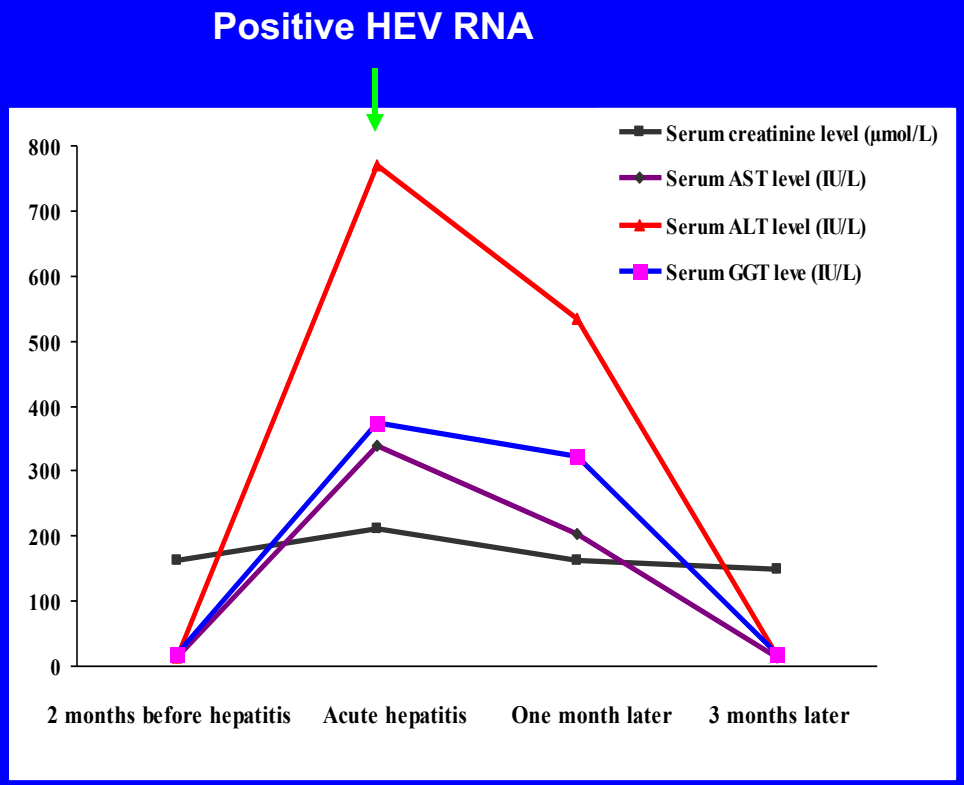
Woolson et al APT 2014

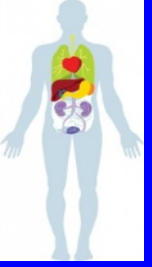
HEV and renal disease

Acute Hepatitis and Renal Function Impairment Related to Infection by Hepatitis E Virus in a Renal Allograft Recipient

Nassim Kamar, MD, Jean Michel Mansuy, MD, Laure Esposito, MD, Florence Legrand-Abravanel, PharmD, Jean Marie Peron, MD, PhD, Dominique Durand, MD, Lionel Rostaing, MD, PhD, and Jacques Izopet, PharmD, PhD

American Journal of Kidney Diseases, Vol 45, No 1 (January), 2005: pp 193–196



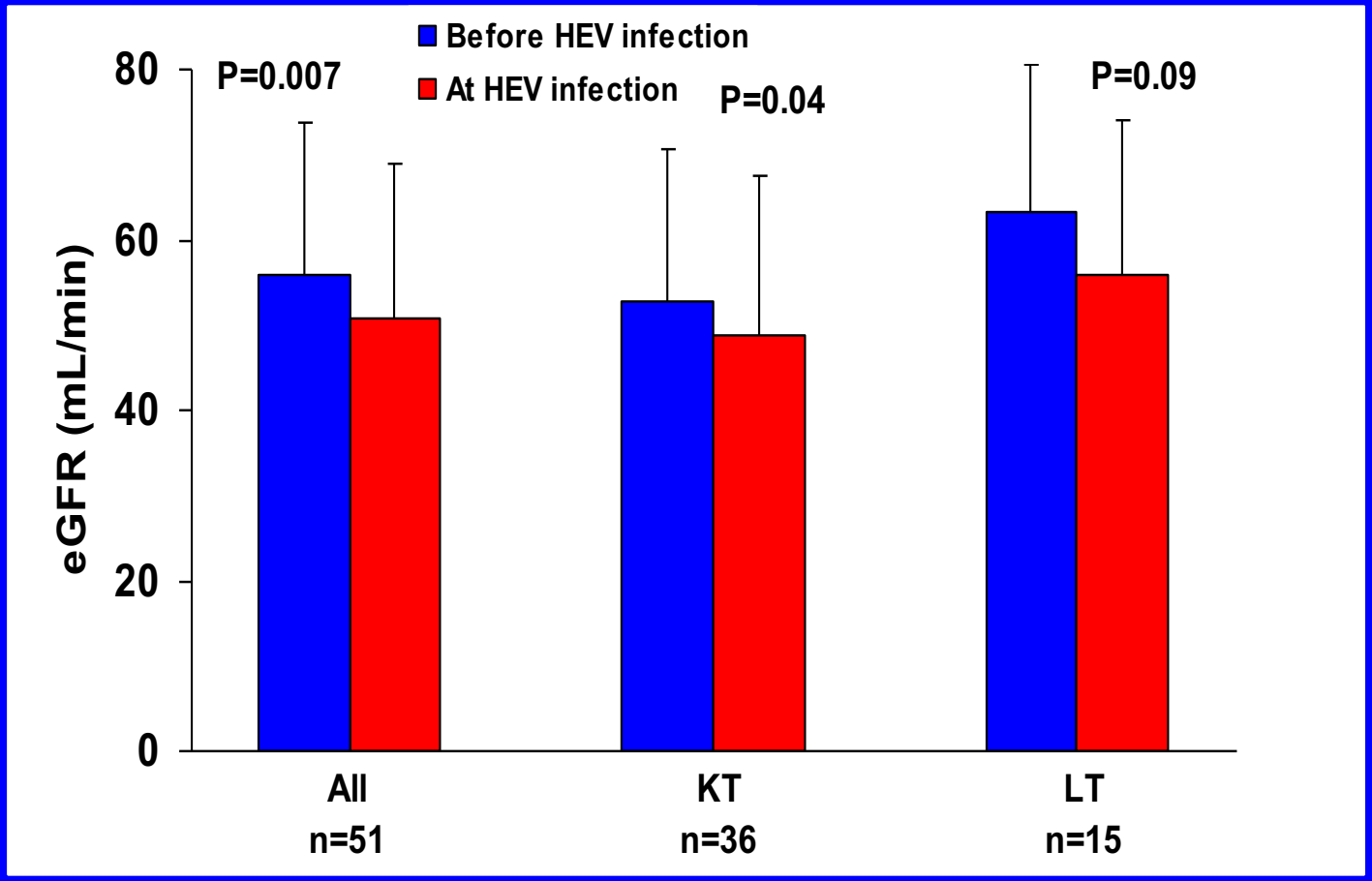


HEV infection and the kidney

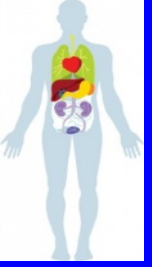
- ✓ Retrospective study
- ✓ 51 SOT patients with HEV infection: 33 KT, 15 LT and 3 SKP
- ✓ Time since transplantation at HEV infection: 56 (1-209) months
- ✓ 48 out of 51 were receiving CNIs-based immunosuppression
- ✓ Among the 51 patients:
  - 22 were cleared of the virus within 6 months (resolving group)
  - 29 patients evolved to chronic hepatitis (chronic group)

Kamar et al., Transplantation 2012

Kidney function at HEV infection



Kamar et al., Transplantation 2012



Kidney histology at HEV infection

- Kidney biopsies were performed in 7 patients at acute phase

- 4 patients with decreased GFR but no albuminuria:
  ⇒ IF/TA grade 1 without features of acute rejection or glomerular disease

- 1 patient with decreased GFR and increased proteinuria
  ⇒ **HEV-induced-MPGN**

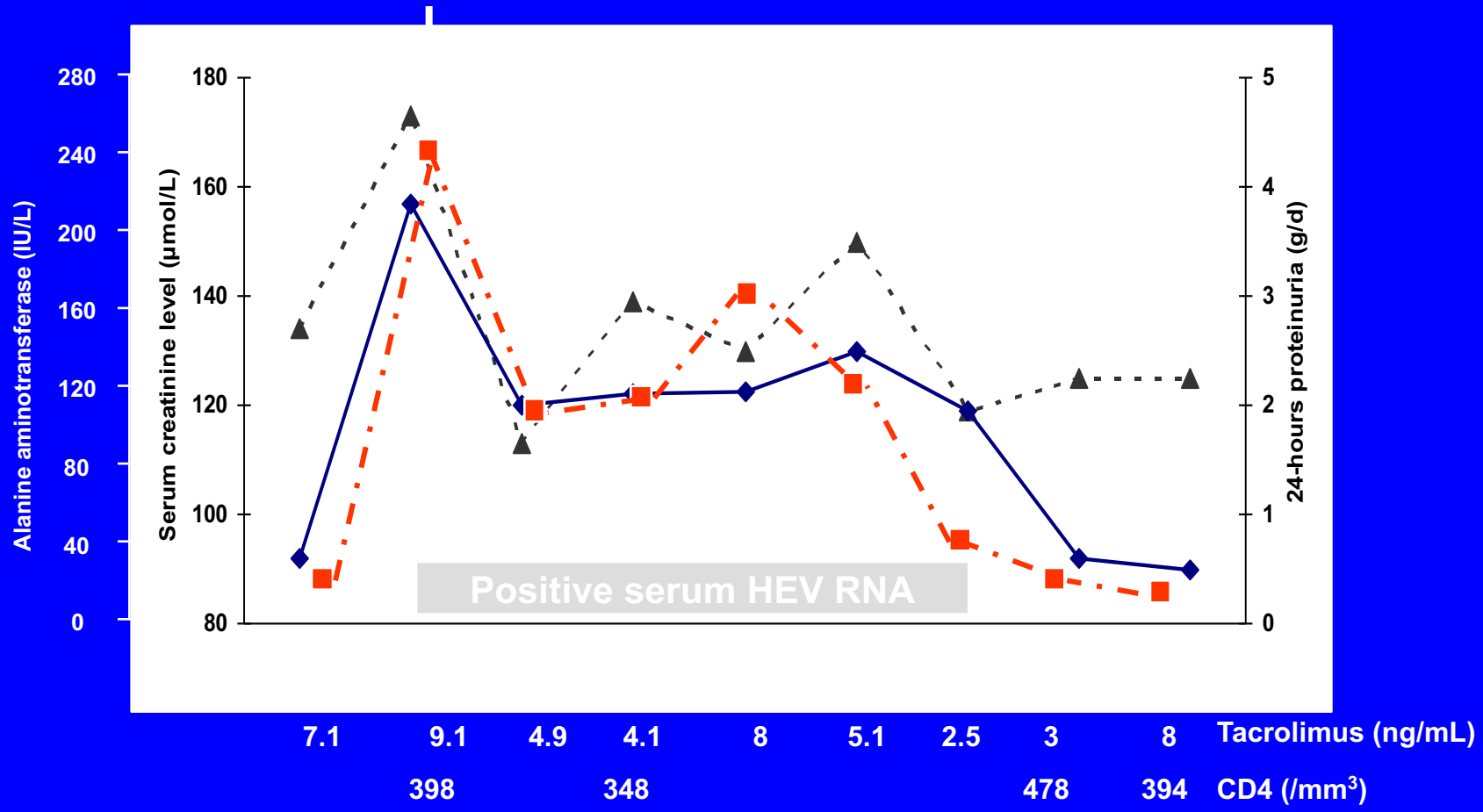
- 2 patients with unchanged GFR but increases proteinuria
  ⇒ Relapse of IgA nephropathy in the presence of a positive cryoglobulinemia (HEV trigger ?)

Kamar et al., Transplantation 2012

HEV-induced MPGN

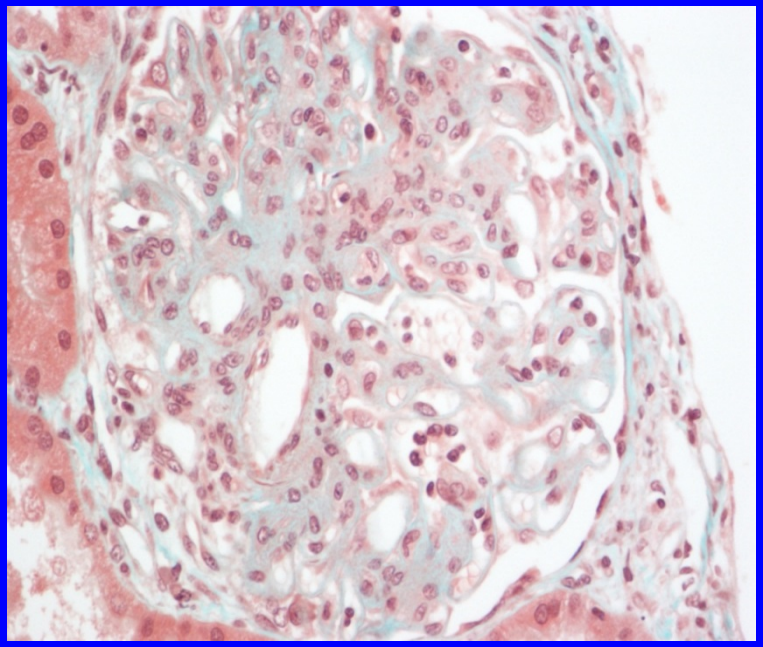
Kidney-transplant patient, second transplantation, sensitized patient

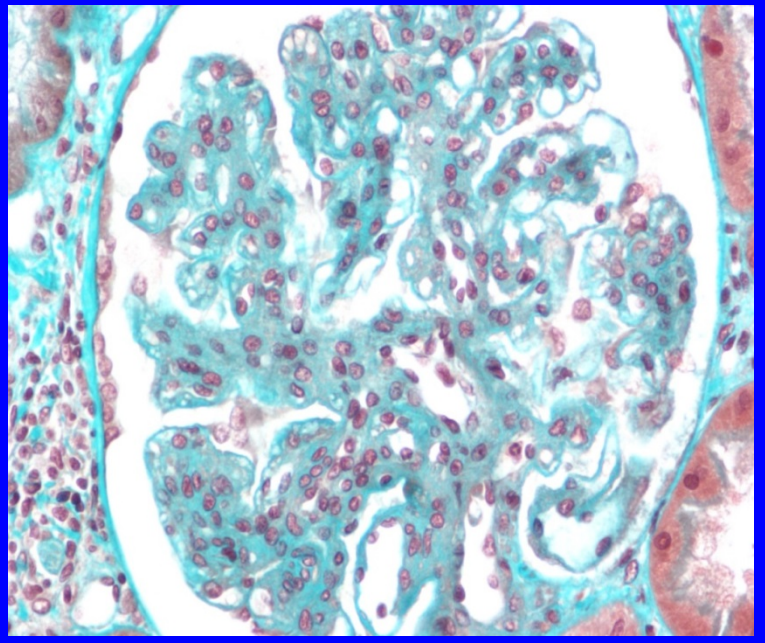
Liver Biopsy: signs of acute viral hepatitis, i.e., A1F1 (Metavir score)
Kidney Biopsy: Features of *de novo* MPGN

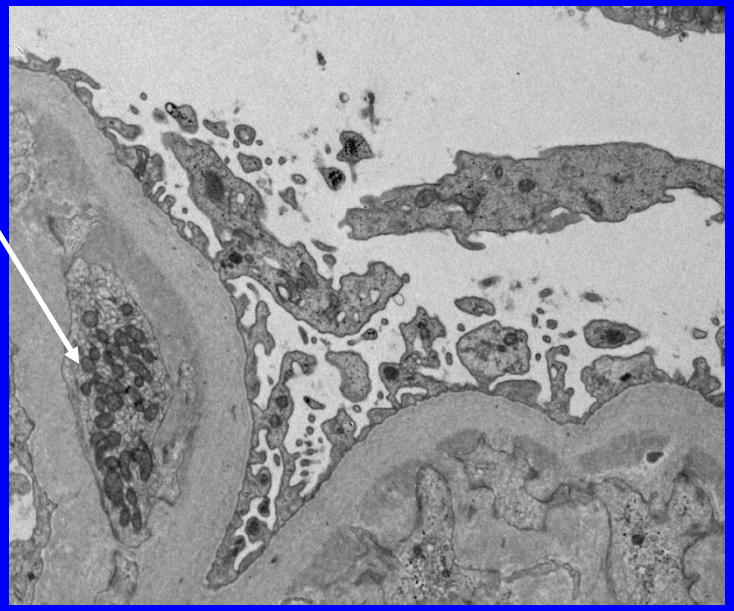


No detected cryglobulinemia or DSAs

Kamar et al., Transplantation 2012

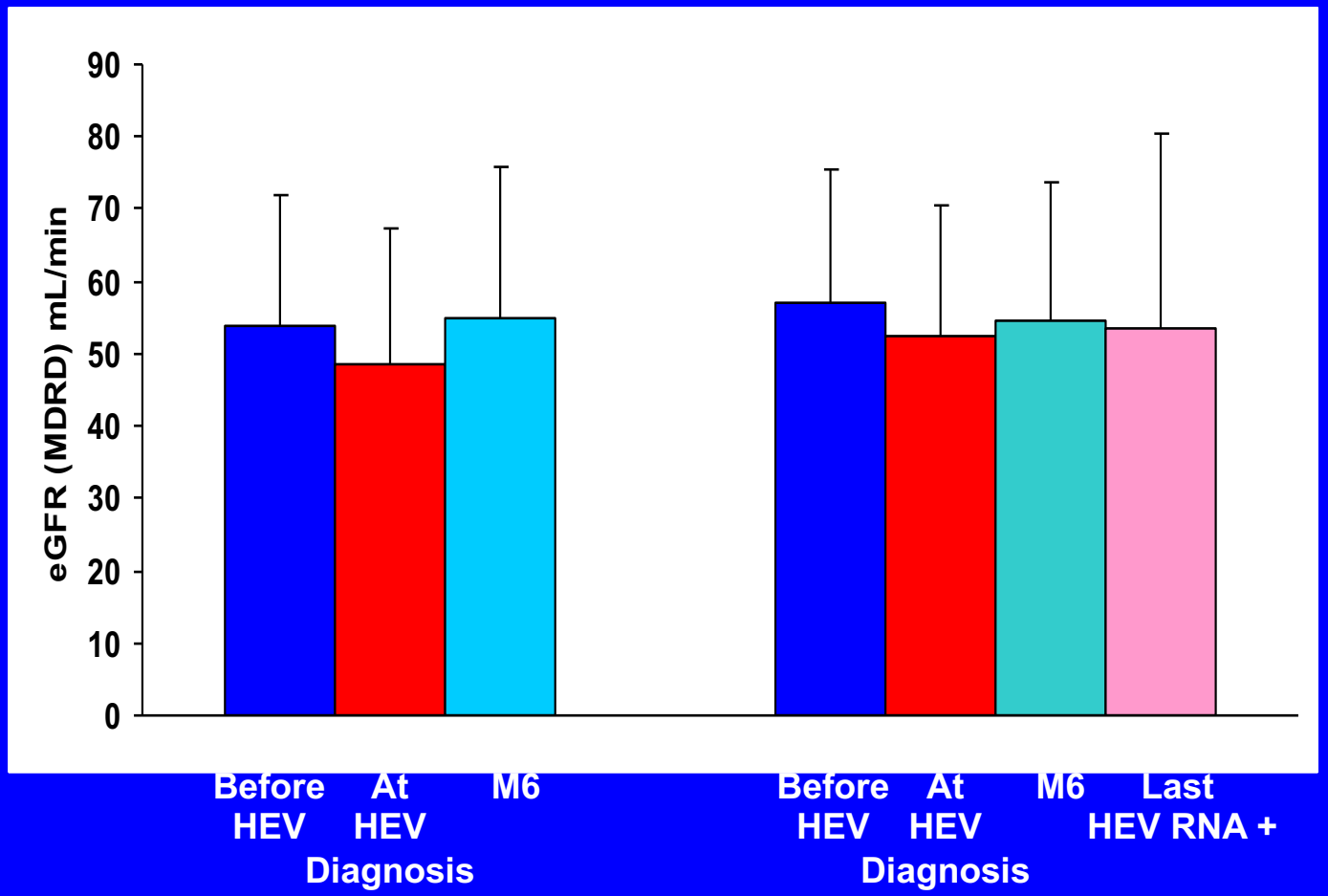






Kamar et al.,
Transplantation 2012

Kidney function in the resolving and chronic groups

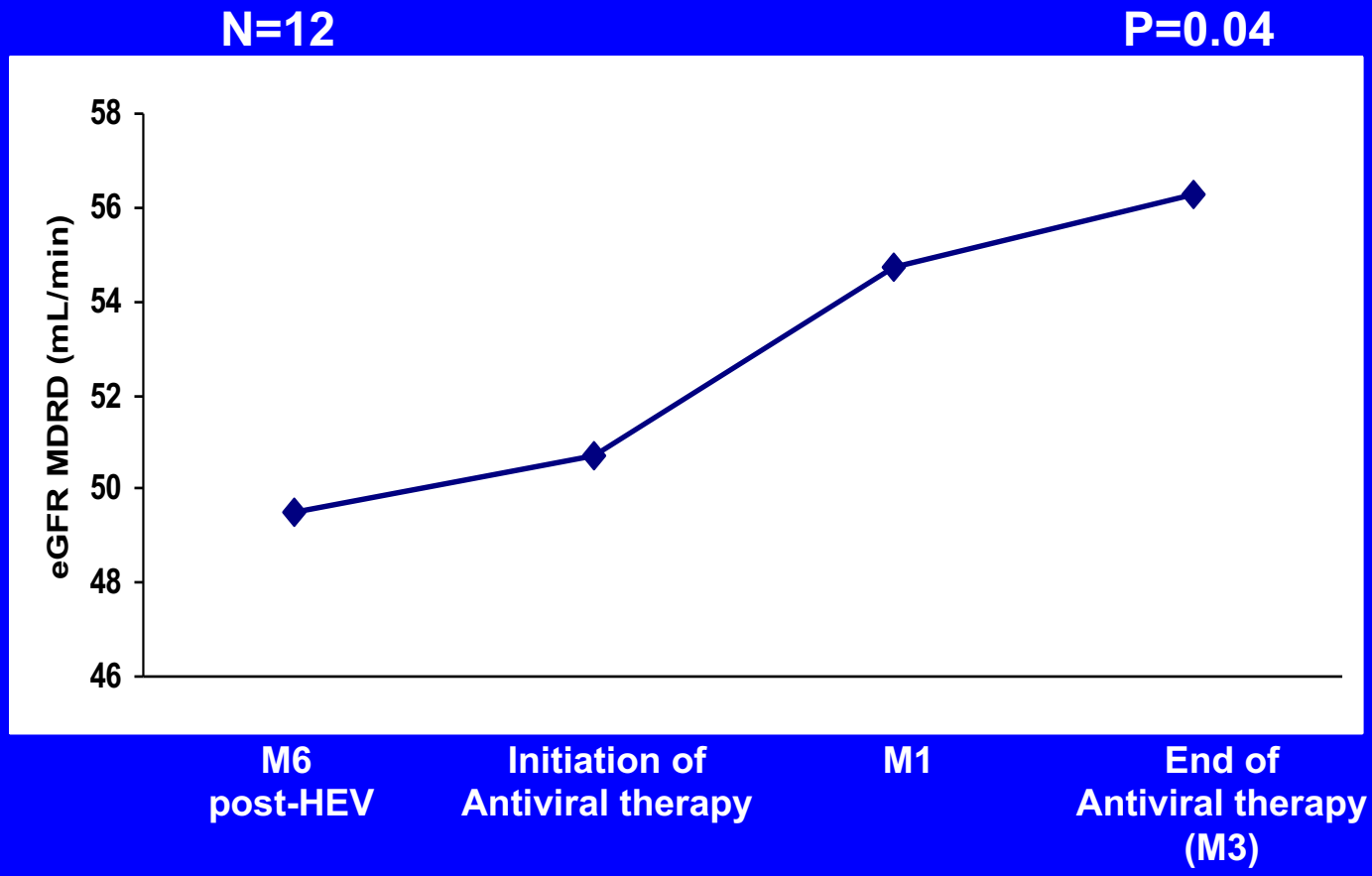


Resolving group (n=22)

Chronic group (n=29)

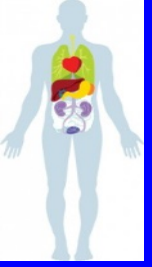
Kamar et al., Transplantation 2012

Kidney function in HEV positive treated patients



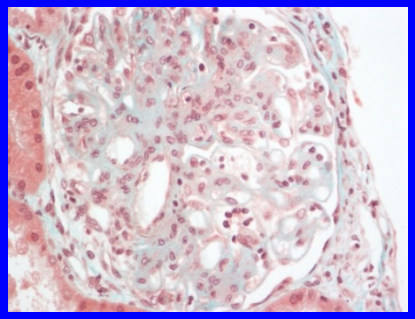
All treated patients were cleared of the virus at month 3
Cryoglobulinemia: 80% at chronic phase vs. 0% after HEV clearance

Kamar et al., Transplantation 2012

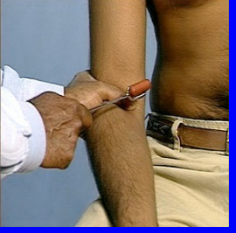


HEV infection and the kidney

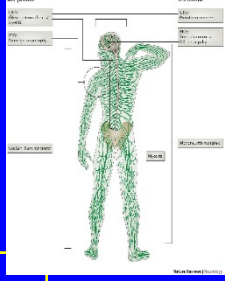
- ✓ Impairment of kidney function at HEV infection
- ✓ Membrano-proliferative glomerulonephritis and membranous glomerulonepritis at acute and chronic phases
- ✓ Cryoglobulinemia that disappears after HEV clearance
- ✓ Regression of nephrotic syndrome after HEV clearance



Ali, Indian J Nephrol 2001
Kamar et al., AJKD 2005
Kamar et al., Transplantation 2012
Taton et al. Transplant Infect Dis 2013



HEV & neurological injury



- 91 cases, worldwide
  - Guillain−Barré syndrome (n=36)
  - bilateral brachial neuritis (n=30)
  - Meningoencephalitis (n=12)
  - Miscellaneous (n=14)
    - Bells Palsy, myosotis, mononeuritis multiplex, vestibular neuritis
- Occurs in:
  - Acute (n=85) and chronic HEV (n=6)
  - Developed and developing countries
- **Neurological symptoms and signs dominate clinical picture**

Kamar et al Emerg Inf Dis 2011, Dalton et al Nature Neurol Rev 2016

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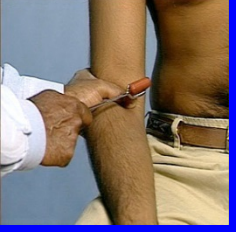
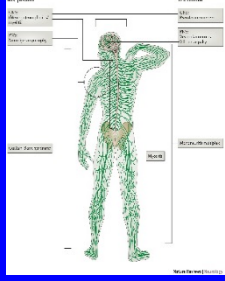


Guillain-Barré Syndrome (GBS)



- Post infectious immune-mediated polyradiculopathy
- Infectious triggers:
  - Campylobacter: 35%
  - Unknown: 50%
- **30% abnormal LFTs ? Cause**

Article

Liver function disturbances in Guillain-Barre syndrome

A prospective longitudinal study in 100 patients

P. G. Oomes, MD, F.G.A. van der Meche, MD, PhD and R. P. Kleyweg, MD, PhD

* SHOW AFFILIATIONS

doi: 10.1212/WNL.46.1.96
Neurology January 1996 vol. 46 no. 1 96-100

Abstract | Full Text | Full Text (PDF)

Also available: Figures Only PPT Slides of All Figures

ABSTRACT

Article abstract-In 100 consecutive patients with Guillain-Barre syndrome, we assessed liver function on admission and at fixed intervals after either intravenous immunoglobulin (IgIV) or plasma-exchange (PE) treatment. On admission, 38% showed a plasma alanine aminotransferase elevation, gamma glutamyl transferase elevation, or both of more than 1.5 times the upper limit of normal. Ten of these patients had serologic evidence of recent cytomegalovirus infection. The remaining 28 patients were negative for other known causes of liver damage, including infection with Epstein-Barr virus or hepatitis A, B, and C; alcohol abuse; hepatotoxic drugs; recent surgery; and concurrent liver disease. In a hospital control group of 100 consecutive patients with subarachnoid hemorrhage, only 5 had unexplained liver function disturbances on admission ($p < 0.0001$). In the IgIV-treated group, the percentage of patients with elevated liver function tests increased from 35% before to 69% shortly after treatment at 2 weeks postadmission ($p < 0.005$). In the PE-treated group, this percentage decreased somewhat from 41% to 36% (not significant). There was also a significant rise in median plasma activity of the various liver enzymes in the IgIV group. At 1 month, however, significant difference had disappeared. At 3 and 6 months, the percentage of patients with liver function disturbances reached a significantly lower level in both treatment groups compared with the time of admission. We concluded that many patients with Guillain-Barre syndrome had mild liver function disturbances without obvious cause. In addition, IgIV treatment was associated with mild transient liver function disturbances through an unknown mechanism.

NEUROLOGY 1996;46: 96-100

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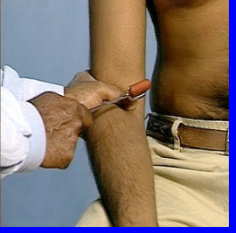
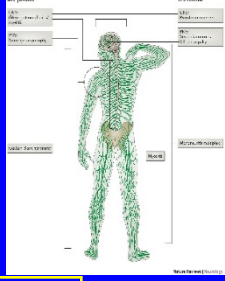
Oomes et al Neurology 1996

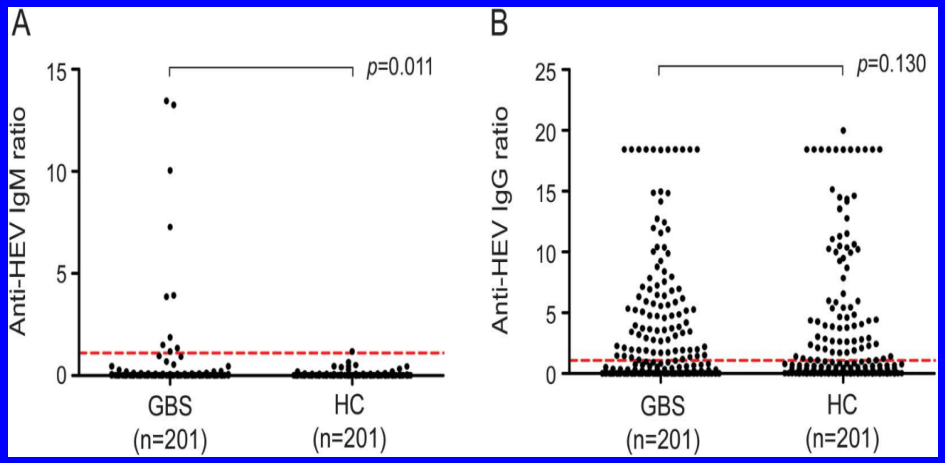


HEV & Guillain-Barré syndrome



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

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



- Mildly abnormal LFT's:
  - normal bilirubin
  - ALT: 70 (range 26-921); abnormal n=7
- Outcome:
  - 1 required ventilation, 7 have significant disability at 6 months
- Some patients are viraemic (HEV3) at presentation
  - ?role for early therapy with ribavirin

van den Berg et al Neurology 2014

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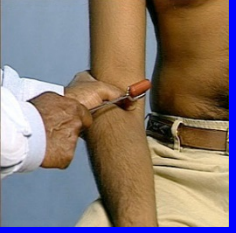
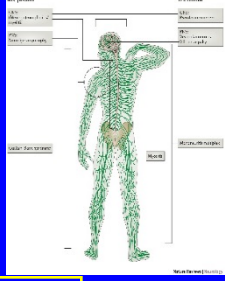
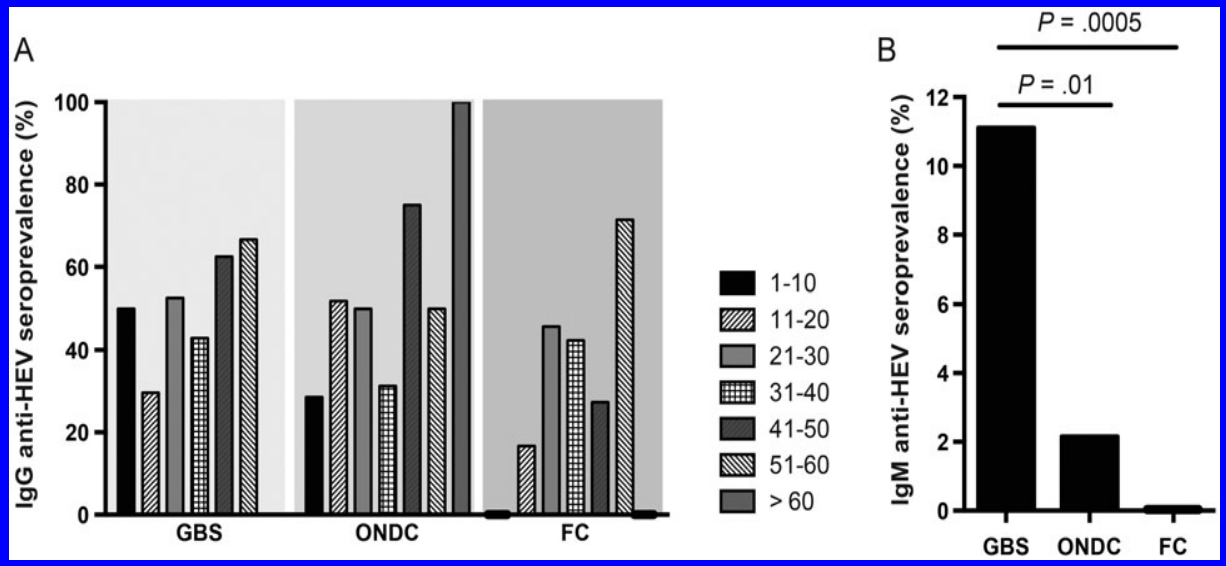


HEV & Guillain-Barré syndrome



Case control study of Bangladeshi patients with GBS (n=100)

- 11% of GBS have HEV infection (HEV genotype 1 n=1)



Geurtsvankessel et al Clin Infect Dis 2013

Worldwide HEV & GBS: n=36

- Age 2-73 years
- 72% male
- All but one: immunocompetent

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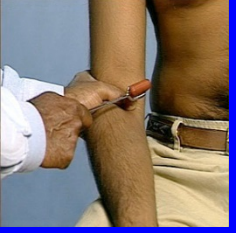
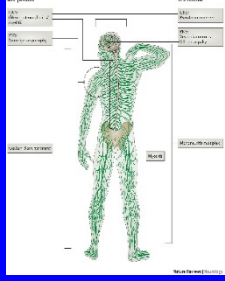


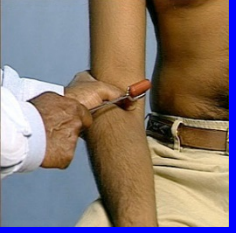
HEV & Neuralgic amyotrophy (brachial neuritis, Parsonage Turner syndrome)



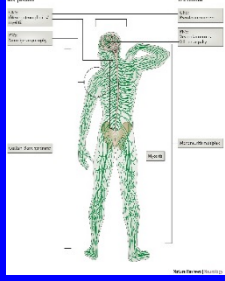
- LFTs abnormal in some patients, ? Cause

- 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 LFT's: ALT 100-300, normal bilirubin
  - 4 PCR positive: HEV genotype 3
- Worldwide HEV & NA: n=30, nearly all from Europe
  - HEV 3
  - Median age 49 years, 88% males
  - Bilateral symptoms +/- phrenic nerve involvement

Van Eijk et al, Neurology 2014



Brachial neuritis and HEV



- Multi-centre international study
  - Cornwall UK, Holland, Germany, Switzerland, France, Italy
- Retrospective
- Brachial neuritis
  - HEV +ve n=57
  - HEV –ve n=61
- Outcome measures
  - Clinical phenotype
  - Clinical outcome

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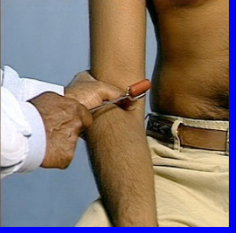
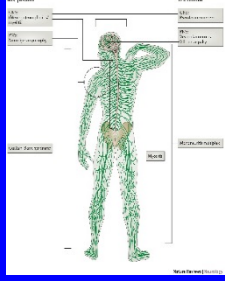


Brachial neuritis and HEV

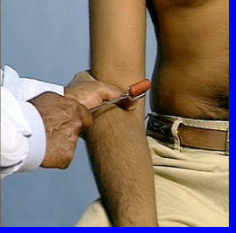


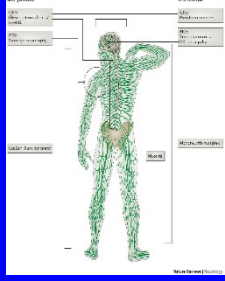
HEV +VE

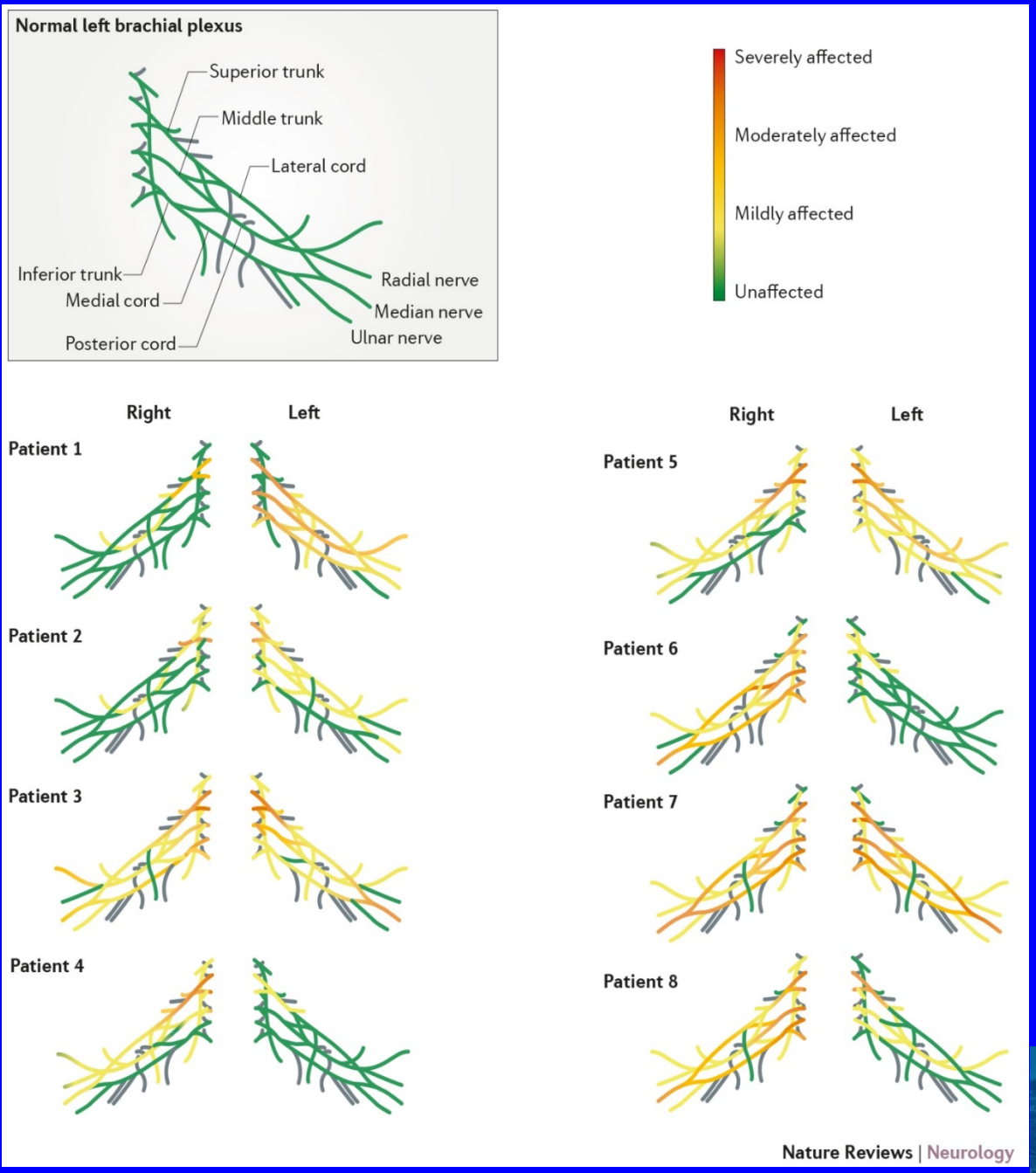
- Age 51 (23-83)
- 82% male
- Bilateral 82%
- Phrenic/lumbar involvement
  - 58%
- Clinical outcome
  - variable

HEV –VE

- Age 44 (25-79) p <0.01
- 75% male NS
- Bilateral 9% p<0.01
- Phrenic/lumbar involvement
  - 10% p<0.01
- Clinical outcome NS
  - variable







Dalton et al Nature Neurol Rev 2016

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Bart Jacobs
Erasmus MC Rotterdam

"Harry. Has this virus been misnamed?"

"These patients have profound neurological injury, but not much of a hepatitis"

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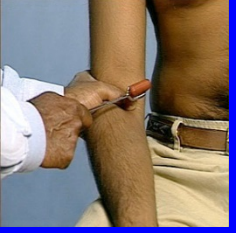
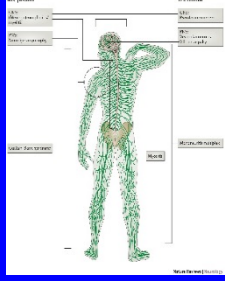


HEV & neurological syndromes: evidence for causality



- Number and homogeneity of cases
  - Over time and geographical location
- Case-control data (GBS) *van den Berg et al, Neurol 2014, Geurtsvankessel et al Clin Inf Dis 2013*
  - Netherlands (HEV3) & Bangladesh (HEV1)
- 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 *Shukla et al PNAS 2011 & J Virol 2012*
  - Strain of HEV incorporating a section of host genome
  - Isolated from pt with HIV and chronic HEV infection
  - Grows on a range of cell lines, including neurological

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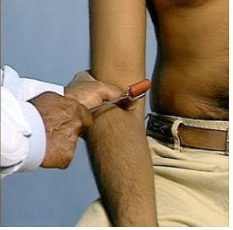
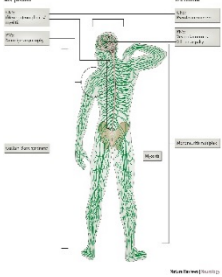
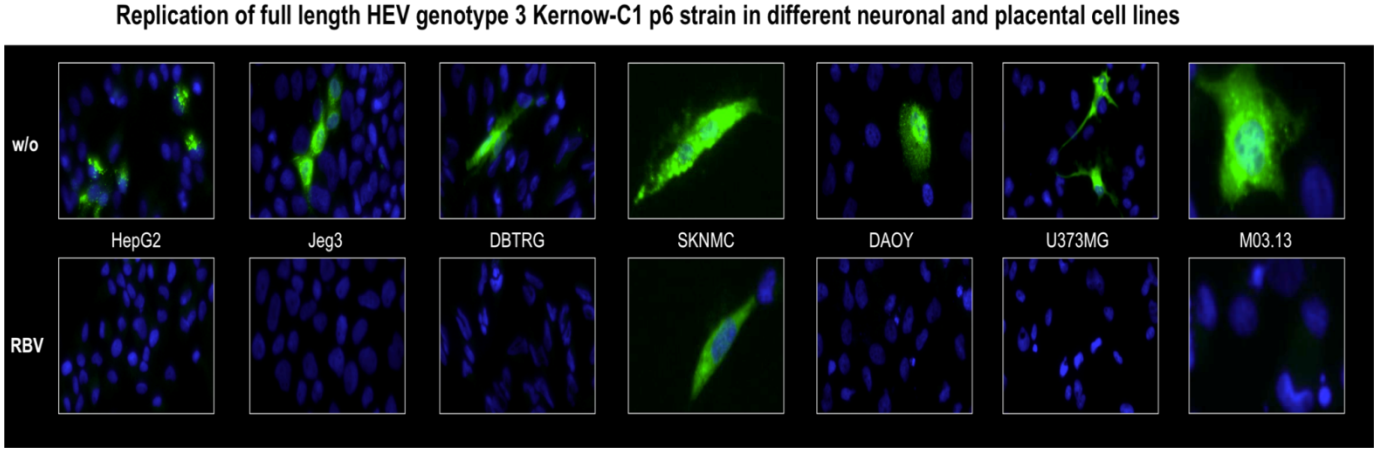


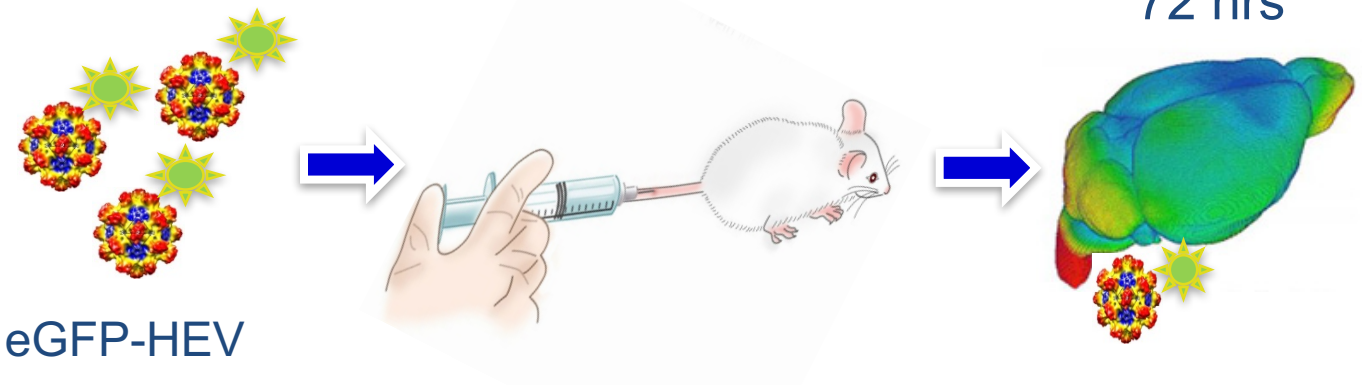
HEV & neurological syndromes: evidence for causality

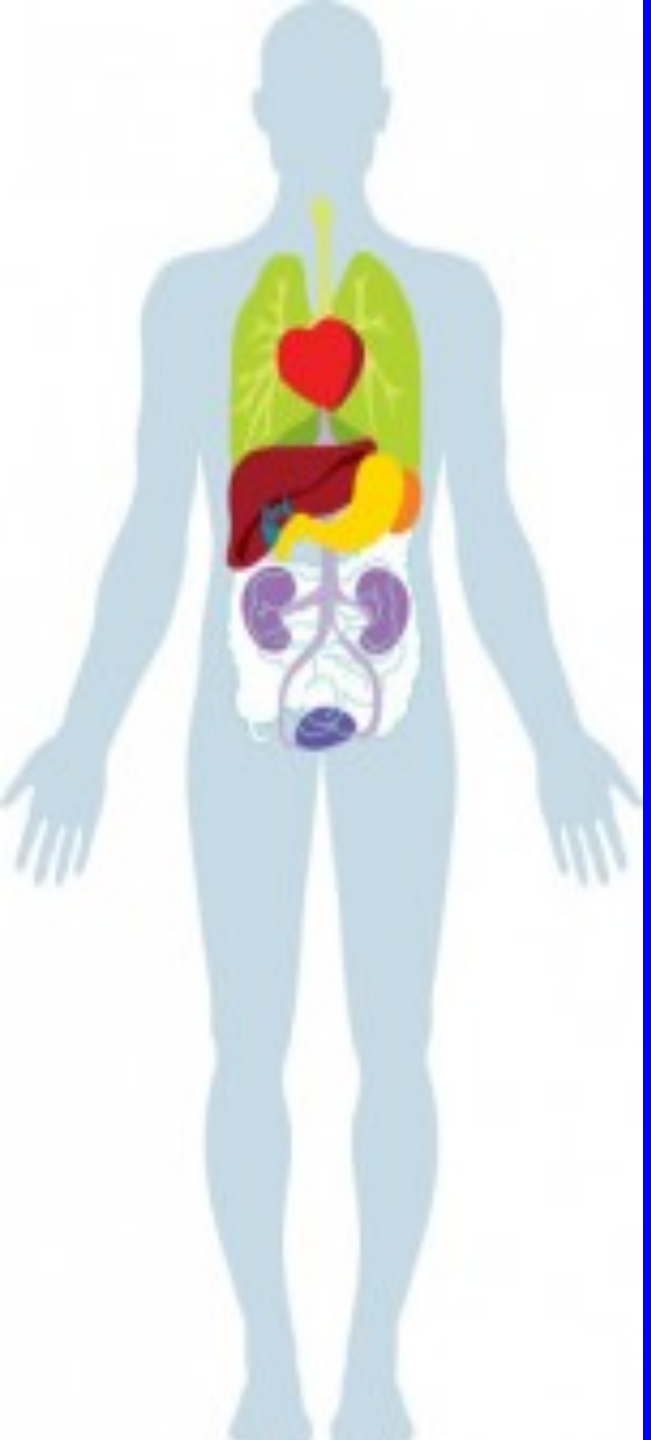


HEV infects neurological cell lines:



HEV crosses blood brain barrier in mice:





Conclusions: extra-hepatic HEV

- Many organ systems affected
- **Association does not equal causation**
- Best evidence for neurological injury
  - Brachial neuritis
  - GBS
- Pathological mechanism uncertain

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Acknowledgments

- Lemon Street Gallery, Truro
- Cain Popovski Smith, Ben Sayer
- Sheila Sherlock Travelling Bursary 2011

- Office of Chief Scientist Scotland
- Duchy Charity
- British Medical Association

Royal College of Physicians
Setting higher medical standards

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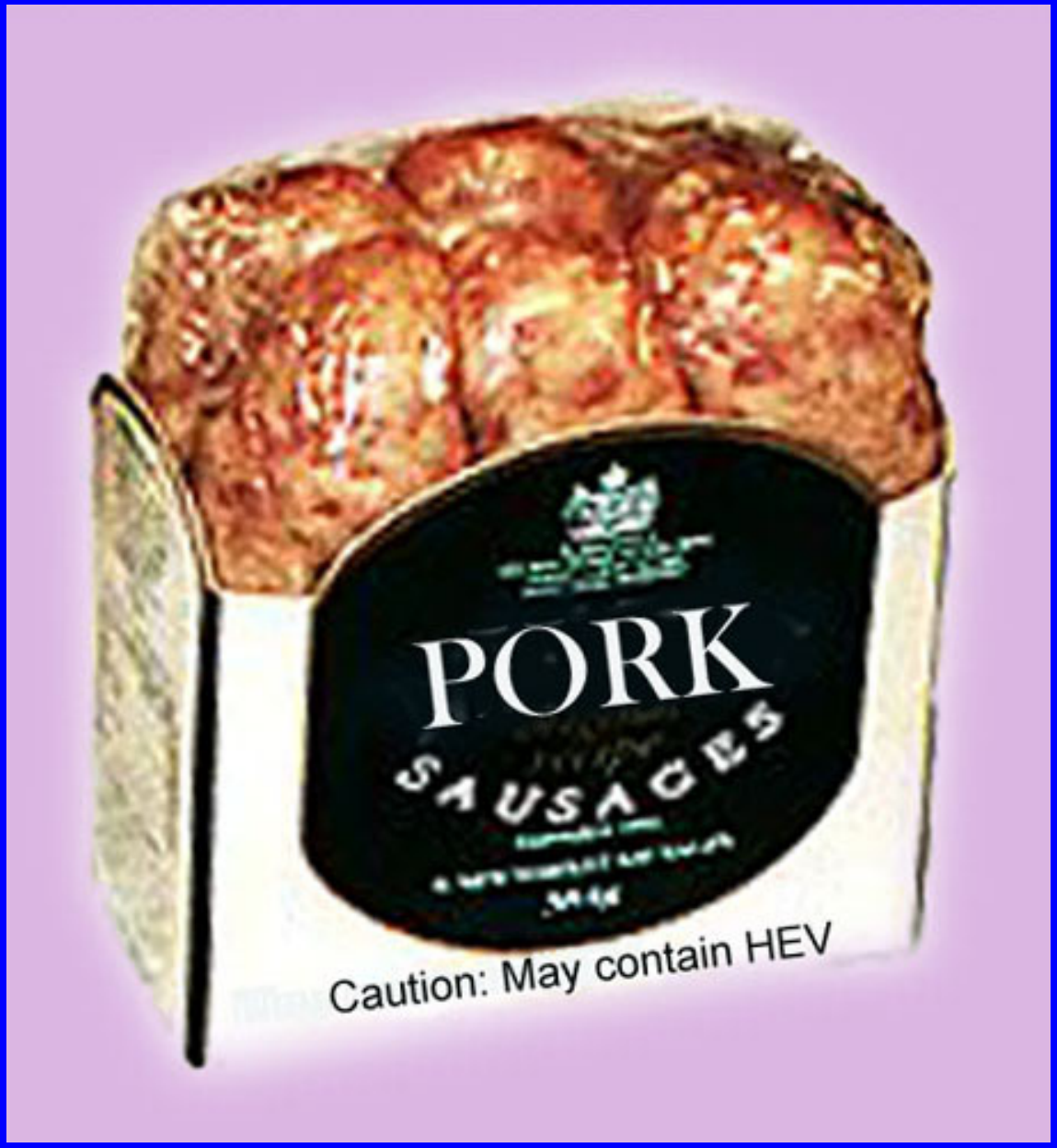
research collaborators

- 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
  - **Bart Jacobs and colleagues, Erasmus MC and Nijmegen, The Netherlands**
  - Hans Zaaijer, Sanquin,Amsterdam, The Netherlands
  - Sven Pischke, Hamburg, Germany
  - Alessandro Bartoloni, Florence, Italy
  - Prof Ningshoa Xia & colleagues, Xiamen University, China
  - **Jacques Izopet, Nassim Kamar & colleagues, Toulouse, France**


PORK
SAUSAGES
Caution: May contain HEV