Hepatitis diagnosis and disease

Viruses in May 2009

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Outline

- Non-invasive fibrosis markers in viral hepatitis
- Genotyping and treatment decisions in HBV
- Utility of RVR in treatment of chronic HCV

Non-invasive markers of fibrosis

- Rationale?
- Liver biopsy
  - Invasive
  - Some risk
    - Pain, anxiety, discomfort (5-20%)
    - Haemoperitoneum, biliary peritonitis, pneumothorax (0.3-0.5%)
    - Death 0.01%
  - Sampling error – 24% in some studies
  - Repeat measurements of fibrosis a challenge

- Serum markers
  - Fibrotest (6 parameters)
  - APRI (aspartate transaminase to platelet ratio index)
- Liver stiffness
  - Transient elastography
  - MR techniques

Transient elastography

- Elasticity - ability to deform under force
- Tissue elasticity can be measured by speed of propagation of transverse shear elastic wave
- Higher the speed, the higher the stiffness
- 50Hz vibration from transducer
- Echo transducer reads
- Samples 1% of organ

- 1-75 kPa reading
- 10 acquisitions
- Intra- and inter-observer COV 3%

- Less reproducible with steatosis, high BMI and lower F stage
- 5-10% measurement failure rate

- Elasticity dependent on
  - Fibrosis
  - Inflammation

- n=327, HCV
- AUROC 0.97 for F4
- AUROC 0.91 for F>=3
- AUROC 0.79 for F>=2

  - Ziol M Hepatol 2005; 41: 48

- Cirrhosis of any cause, n=711
- kPa 17.6
- AUROC F4 0.96
- Sensitivity 77%
- Specificity 97%
- PPV 91%
- NPV 92%
  - Foucher Gut 2006; 44: 403

Fibrotest

- Meta-analysis
- n=3282
- F2,3,4 vs. F0,1
- AUROC 0.84
- Between stages eg. F1 vs. F2 0.62-0.69

  - Poynard BMC Gastro 2007; 7: 40

? Combine TE and Fibrotest

- TE and Fibrotest performed similarly, better than APRI
- TE and FT together
- AUROC F4 0.95

- Castera Gastro 2005; 128: 343

Role of non-invasive markers

- Screen for risk of large varicies
  - Foucher Gut 2006; 55: 403
- Decide re HCC screening in patients unwilling for biopsy
- Doesn’t completely replace biopsy
  - Alternate diagnoses
  - More reliable in middle stages
- Useful at extremes of fibrosis

HBV genotype in treatment

HBV Rx outcome baseline factors

- Lower HBV DNA
- HIV coinfection
- HBeAg+
  - Increased necroinflammatory activity
- HBeAg-
  - Young, female
- PEG-IFN
  - Higher ALT and lower HBeAg level
- Adefovir - weight

HBV genotypes

- Treatment response
- Mainly interferon based therapy
- Not much evidence with nucleoside antivirals
  - ? adefovir

Geographic distribution

A Northwest Europe, North and Central America

B Indonesia, China, Vietnam

C

East Asia, Korea, China, Japan, Polynesia, Vietnam

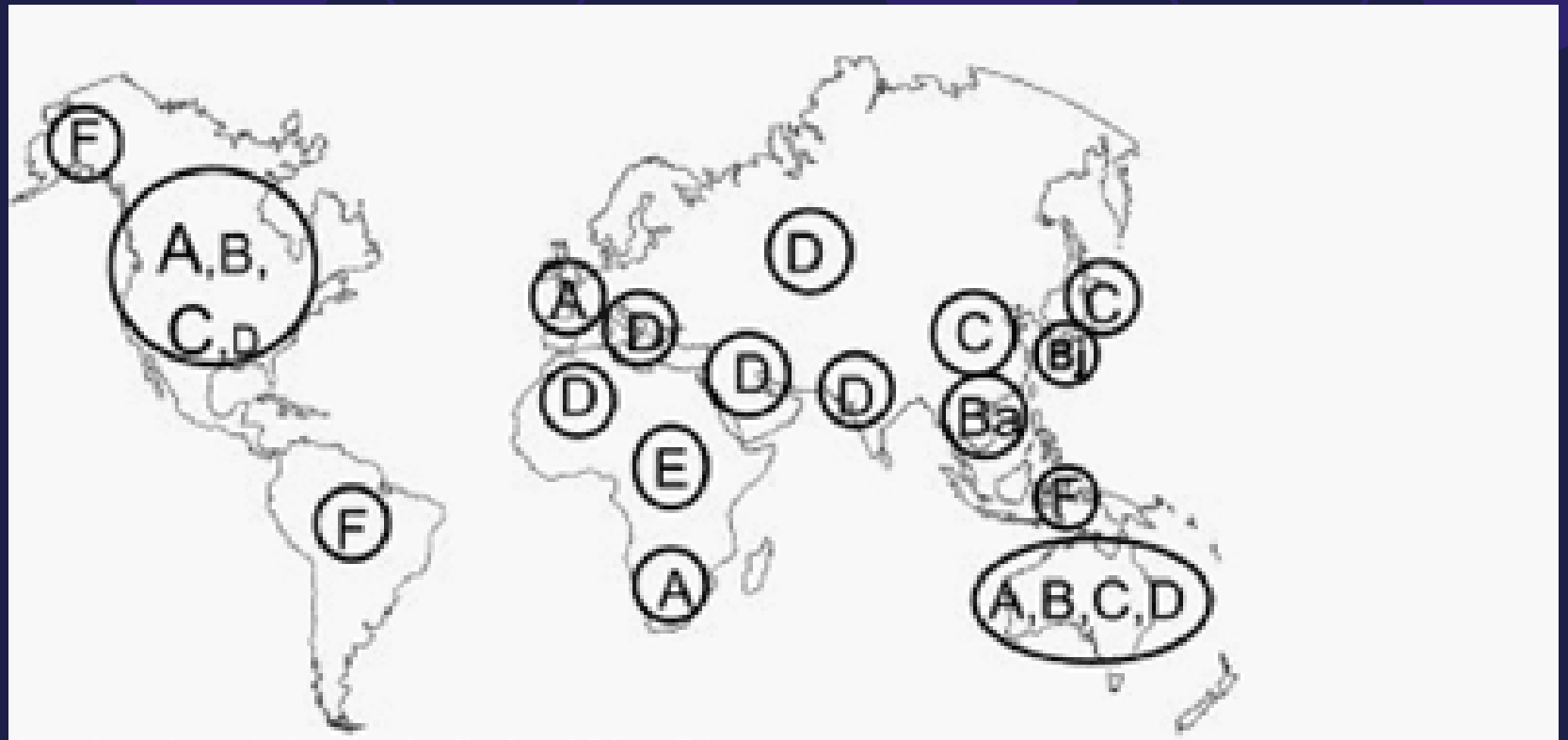
D Mediterranean area, Middle East, India

E Africa

F Native Americans, Polynesia

G United States, France

H Central America



American Association for the Study of Liver Diseases

Figure 1. Geographic distribution of hepatitis B virus genotypes.

Fung and Lok, Hepatology 2004

HBV genotype response – IFN-alpha

- Chinese
- n=109, retro analysis of RCT
- all patients
  - B (39%) vs C (17%) - treated
  - B (10%) vs C (8%) - untreated controls
- n=66 with elevated ALT
  - B (57%) vs C (21%) - treated
  - B (25%) vs C (8%) - untreated controls
    - Wai CT, et al Hepatol 2002; 36: 1425

Untreated clearance rates different

- Spain
- A (n=134) > D (n=90)
- Log rank 4.6
  - Sanchez-Tapias JM et al Gastro 2002; 123:1848

HBV genotype response – IFN-alpha

- Taiwan
- n=58
- HBeAg seroconversion
- B 41% vs. C 15%
- Younger age also a factor in outcome
- No untreated controls
  - Kao JH Gastro 2000; 118: 554

HBV genotype response – IFN-alpha

- Germany
- n=64
- A (37%) > D (6%)
- Low viral load and core promoter region mutations also associated with outcome
  - Erhardt A, et al Hepatol 2000; 31: 716

HBV genotype response – IFN-alpha

- European cohort
- n=103
- Genotype A OR 6.2 of short treatment response (16W)
  - greater than ALT or HBV DNA
    - Hou et al J Med Virol 2007; 79: 1055

HBV genotype response – IFN-alpha

- Germany
- n=144
- SVR

Geno	HBeAg +	HBeAg -	All
A	46%	59%	49%
D	24%	29%	26%

- ALT also predictive of response
  - Erhardt A et al Gut 2005; 54: 1009

HBV genotype response – PEG-IFN

- Multinational, n=266
- PEG IFN vs PEG IFN + 3TC
- HBeAg seroconversion
- A 47%
- B 44%
- C 28%
- D 25%
  - Janssen et al Lancet 2005; 365:123

HBV genotype response – PEG-IFN

- N=814

	PEG IFN		PEG+3TC		3TC	
A	23	52%	18	22%	15	20%
B	76	30%	82	29%	73	23%
C	162	31%	156	28%	162	18%
D	9	22%	11	18%	17	18%

- ? A > B,C,D – but PEG+3TC group
  - Lau GKK, NEJM 2005; 352: 2682

HBV genotype response – PEG-IFN

- N=518, geno A-D
- HBeAg neg
- PEG-IFN vs PEG-IFN + 3TC
- B vs. D OR SVR 3.69
- C vs. D OR SVR 5.46
  - Bonino F, Gut 2007; 56: 699

Conclusion – HBV genotype testing?

- Some inconsistency in response data, BUT probably A>B>C>D
- Probably test genotype if PEG-IFN treatment being considered
- Information may aid decision for patient re PEG-IFN vs. nucleoside treatment

HCV treatment response predictors

- Baseline
  - Ethnicity – Asian>white>black
  - Age - younger
  - Gender - female
  - Lower BMI
  - Less or no steatosis
  - Host genes
  - Less fibrosis, no cirrhosis
  - Lower viral load
  - Genotype 2,3 vs 1

HCV RNA tests on treatment

- RVR – rapid – 4 weeks
- EVR – early – 12 weeks
- LVR - 24 weeks – if EVR <2 log but not undetectable
- SVR – sustained – no virus 6 months after end of treatment (usu. 24 or 48 W)

RVR as predictor of SVR

- PEG-IFN-alpha 2a or 2b

n	Genotype	OR	Ref
740	1	23.7	Jensen Hepatol 2006; 43:954
428	2,3	4.2	Dalgard Hepatol 2008; 47: 35
13831-4		7.5	Fried J Hepatol 2008; 48: 5A

86-100% predictive of SVR regardless of genotype

RVR and reduced therapy duration

- n=200, genotype 1
- PEG-IFN and weight based RBV

Weeks	SVR	RVR n=87	Low VL + RVR (n=52)
48	79%	100%	100%
24	59%	89%	96%

- Yu ML Hepatol 2008; 47:1884

RVR and reduced therapy duration

- Asian, genotype 1, n=308

Week	SVR	RVR +	No RVR Low VL	EVR
48	76%	100%	35%	44%
24	56%	94%	16%	20%

- Liu CH, Clin Infect Dis 2008;47:1260

RVR and reduced therapy duration

- Geno 2 and 3, n=283
- 12 vs 24 weeks, weight based RBV dose
- RVR 64%
- 76 vs 77% SVR
- Geno 2 80% SVR
- Geno 3 66% SVR

- Mangia A NEJM 2005; 352: 2609

RVR and reduced therapy duration

- Genotype 2 and 3, n=1469
- RBV dose was 800mg

Weeks	SVR	Low VL	RVR
24	70%	81%	85%
16	62%	82%	79%

- Shiffman ML, NEJM 2007; 357: 124

RVR and reduced therapy duration

- Geno 3, n=113
- Treated for 16 weeks vs 24 weeks based on RVR
- Those with high VL had lower SVR (59% vs 85%)

  - Von Wagner M Gastro 2005; 129: 522

? Short course and retreat

- Genotype 2 and 3, n=718
- Weight based dose RBV
- 69% RVR
- Of these 83% SVR with 12-16 weeks Rx
- Platelets <140, BMI>30 predict relapse
- 43/67 retreated with 70% achieving SVR
- Therefore, 12 weeks for RVR, not advanced fibrosis, normal BMI
  - Mangia A Hepatol 2009; 49:345

Conclusions

- Patients
  - receiving weight based dosing of ribavirin
  - achieving RVR
  - with a low baseline viral load
  - may be able to be treated for a shorter duration
  - and retreatment may have an acceptable response rate (in geno 2 and 3)
- Studies of longer treatment for no RVR

Conclusions

- Transient elastography moving into practice
- HBV genotyping possibly useful if HBV treatment decisions
- HCV treatment associated RVR with low baseline VL may allow short duration Rx