Viruses causing hepatitis outside the alphabet
EBV, CMV, HHV6 and beyond

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What did the Flintstones teach us?
What were the names of the main characters?
What were some of the prehistoric gadgets?

1. What is hepatitis
   • Aetiology
   • Clinical, virological
2. Hepatitis due to CMV
   • Disease pathogenesis
   • Clinical
3. Hepatitis due to EBV
   • Pathogenesis
   • Clinical
4. Hepatitis due to other viruses
   • principles
5. Diagnosis
   • Laboratory principles

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Hepatitis

- Syndromic diagnosis
  - Hepatitis = ‘inflammation of the liver’ and not a single disease
- Aetiology
  - Viruses
    - Drugs
    - Secondary manifestation of systemic illness
    - Connective tissue diseases
    - Other agents
- There are 15 virus families infect and damage hepatocytes, most have 1-2 species only

Hepatitis definitions

- Acute: Short term
- Chronic: Lingering or lasting > 6 months, can be severe
- Fulminant: Develops quickly, high mortality rate
- Cirrhosis: Hepatic scarring any cause
- Jaundice: Yellowing of the skin, eyes due to raised levels of bilirubin in the blood due to liver damage

Hepatitis epidemiology

- Acute viral hepatitis is common
- Annual incidence of viral hepatitis
developed countries is 0.25 per 1000 population underestimate - correct figure 1-2 cases per 1000higher in developing countries
- Mortality overall is 1% for hepatitis infectionhigher in older people, especially fulminant disease

Hepatitis – acute viral

- Due to all forms of hepatitis virus
- Hepatitis A, EBV, CMV and HHV6 only cause acute hepatitis.
- Presentation with malaise, anorexia, nausea, vomiting, RUQ pain or asymptomatic
- Examination jaundice dark urine pale stools

Outlines

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**Herpesvirus Subfamilies**

<table>
<thead>
<tr>
<th>Sub-family</th>
<th>Host Range</th>
<th>Growth Cycle</th>
<th>Cytopathic Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV1, 2, VZV</td>
<td>Variable Broad</td>
<td>Short</td>
<td>Cell lysis</td>
</tr>
<tr>
<td>CMV, HHV6, 7</td>
<td>Restricted</td>
<td>Long</td>
<td>Cytomegalia</td>
</tr>
<tr>
<td>GBV, HHV8</td>
<td>Restricted</td>
<td>Medium</td>
<td>Cell lysis</td>
</tr>
</tbody>
</table>

**Phases of herpesvirus infection**

- **Primary infection**
  - Lytic gene expression
  - Infectious virus released

- **Latency**
  - Limited gene expression
  - No infectious virus

- **Reactivation**
  - Latent virus activated
  - New progeny infectious virus

**CMV Transmission**

**CMV Clinical Disease**

- Immunocompetent individuals
  - Asymptomatic, mononucleosis
  - Reactivation and reinfection

**CMV Clinical Disease**

- Immunocompromised individuals
- HIV AIDS patients
- Transplant patients
  - Reactivation of previous infection and primary infection by donor strain

- GIT disease, CNS encephalitis, retinitis, hepatitis, myocarditis, pancreatitis, organ rejection and pneumonitis

**CMV hepatitis clinically**

- Usually associated with mononucleosis (not always)
- Usually asymptomatic
- Granulomatous hepatitis
  - Also fever, vomiting
  - Large numbers of atypical lymphocytes (50%)
CMV hepatitis pathology

- Mononuclear portal and sinusoidal infiltrate,
- Increased hepatocellular mitotic activity
- Minimal hepatocellular necrosis
- Less commonly
  - granuloma formation
  - bile duct epithelial damage
- Typical CMV nuclear inclusions and CMV antigen identified 1/6
- Large numbers CD8+ cells (persistence) or NK cells (clearance)

EBV clinical presentation

- Usually subclinical childhood
- 90-95% adults seropositive
- 50% of <5 yrs seropositive
- Glandular fever
- Haematologic presentation
  - Haemolytic anaemia AIHA
  - Thrombocytopaenia
- Splenic rupture
- CNS <1%
  - Encephalitis
  - Guillain Barre
  - Bell's palsy
  - Transverse myelitis

EBV hepatitis pathology

- Liver
  - Mild changes
  - Hepatocyte swelling, vacuolization minor
  - Lymphocytes and monocytes periportal
  - Biliary stasis rare
- CNS
  - Alterations in fatal cases
  - Neuronal degeneration, mononuclear infiltration minor, astrocyte proliferation
  - Generalised

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EBV clinical presentation

- Hepatitis presentation
  - Usually biochemical hepatitis
  - Asymptomatic elevation of AST, ALT, GGT
  - Present in 85% of patients
  - Jaundice rare
- Severe hepatitis
  - Carcinosis, hepatic failure rare
  - Severe unlikely
- Other complications
  - Cardiac rare myo/pericarditis
  - Respiratory rare unsubstantiated
  - Death rare
  - Tumours OHL, Burkitt's Hodgkin's, NPC
EBV virology
- Gamma-1 herpesvirus
  - Infects epithelial cells, ? then B lymphocytes
  - Marked CTL response seen as atypical monos
  - Binds CD21(C3d complement receptor) via envelope gp350 + MHCII via gp42
  - Latency in B cells (1-50 per 106 cells)

EBV virology
- Gamma-1 herpesvirus
  - EBV driven B lymphocyte proliferation/immortalisation
  - Episomal maintenance
  - Type A and B indistinguishable serologically
  - Different proteins expressed during latency LMP1, LMP2, EBNA x 6, EBER x 2

EBV virology
- Shedding oropharynx
  - Healthy adults 10-25%
  - Infectious mononucleosis syndrome 50-100%
  - HIV-1 infected 50%
  - Renal tx recipients 50-70%
- Spread
  - Intimate contact
  - Not recovered from fomites
  - Post pump syndrome (most CMV)

EBV Serology
- Potential cross-reactivity with HAV
  - HAV IgM co-detected with EBV IgM in 9/15 cases [Naveau 1985]
  - 4/5 were RA +ve
  - EBV IgM acute hepatitis, 0/5 HAV IgM +ve [Naveau 1985]
  - EBV reactivation during HAV [Ritter 1996]
- Potential cross-reactivity with autoimmune
  - EBV +ve post AIH in 7/13 [Vento 1995, Cabibi 2008]
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Other viruses

- 15 families
- Herpesviruses
  - HHV6
  - VZV
- Adenovirus
- Flaviviruses
  - Dengue, Yellow fever (HCV)
  - Aksuca virus, Kyasanur Forest disease, Omsak
  - Hemorrhagic fever
- Picorna
  - ECHOvirus (HAV)
- Arenaviruses
  - Guanariot, Junin, Lassa fever, Lujo, Mchuip, Sabia

Other viruses

- Bunyaviruses
  - Crimean-Congo hemorrhagic fever, Dobrava, Hantaan, Pumala, Rift Valley fever, Seoul, SFTS
  - VZV
- Coronaviruses
  - SARS
- Erythrovirus
  - Parvovirus B19
- Filoviruses
  - Ebola, Marburg
- Orthomyxoviruses
  - Influenza
- Reoviruses
  - Colorado tick fever, Reovirus
Viral hepatitis investigations

- **General**
  - liver tests (bilirubin, AST, ALT, GGT)
  - bleeding studies
  - exclusion of non viral causes
  - rule out mechanical obstruction (abdominal US, CT)

- **Specific tests**
  - HAV (IgM, IgG)
  - HBV (HBsAg, HCV Ab, HBe Ag, DNA PCR)
  - HCV (Ab, PCR)
  - HDV (HBsAg, HDV Ab)
  - HEV (western blot)
  - CMV (IgG IgM IgG avidity)
  - EBV (IgG IgM IgG avidity)
  - HHV6 (PCR)

What did the Flinstones teach us?

How to smoke Winston cigarettes in the closing credits

What were the names of the main characters?
What were the names of the main characters?
Fred
Wilma
Pebbles Flinstone-Rubble (nee Flinstone)
Barney Rubble
Betty Rubble
Bamm-Bamm Rubble

What were some of the prehistoric gadgets?
a baby woolly mammoth used as a vacuum cleaner
an adult woolly mammoth acting as a shower by spraying water with its trunk
elevators raised and lowered by ropes around brontosaurus' necks
"automatic" windows powered by monkeys on the outside
birds acting as "car horns," sounded by the driver pulling on their tails or squeezing their bodies
an "electric" razor made from a clam shell, vibrating from a honey-bee inside
a pelican as a washing machine, shown with a beakful of soapy water
a woodpecker whose beak is used to play a gramophone record

What was the town where they lived called?
What was the other name for the town where they lived?
BEDROCK
ROCKVILLE
Blood Supply testing

- Mainly viral
- Ignores persistent non-threatening viruses
- Constantly changing
- Role of emerging viruses

<table>
<thead>
<tr>
<th>Hepatitis</th>
<th>Acute</th>
<th>Chronic</th>
<th>Fulminant</th>
<th>Cirrhosis</th>
<th>HCC</th>
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<td>+</td>
<td>0</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
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<tr>
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<td>+</td>
<td>60%</td>
<td>-</td>
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</tbody>
</table>

What are the names of the seven dwarves, and what was the woman.

Dopey, Grumpy, Doc, Happy, Bashful, Sneezy, Sleepy

An only child, maternal death, somnolence, hallucinations
Queen you are full fair, 'tis true, but Snow White is fairer than you
The fairest of them all