

## Hepatitis

i.e. inflammation of the liver

### Symptoms:

- Asymptomatic
- Jaundice if severe

### Laboratory findings:

- Abnormal **LFTs**, typically raised AST and ALT.
- Polyclonally raised **immunoglobulins**
  1. Only IgA raised – seen in liver disease, particularly due to alcohol, as damage to liver impairs role in IgA metabolism.
  2. Raised IgG and IgA – indicates persistent infection or inflammation.
  3. Raised IgM – seen in Primary Biliary Cirrhosis, and also recent infection, particularly viral.

- Disease of copper metabolism with excessive deposition of copper in tissues e.g. eyes, liver, kidney, brain
- Chronic hepatitis and may have neurological complications.
- Autosomal recessive inheritance of mutations in ATP7B gene, disrupting copper excretion.
- Prevalence of 1:30,000 worldwide.

### Laboratory investigations:

- Plasma **copper** (low) – not very specific.
- Serum **caeruloplasmin** (v low) – 90% sensitive.
- Examine eyes with slit lamp to look for Kayser-Fleischer rings in the cornea.
- Liver biopsy (if possible) showing high copper deposition.
- Penicillamine test (10-20 fold increase in urinary copper 24h post-penicillamine).

## Wilson's disease

## α1-antitrypsin deficiency

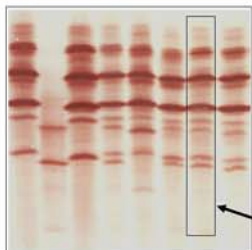
- Pulmonary and/or liver disease, presenting at any age, even neonate.
- Pulmonary disease e.g. chronic obstructive pulmonary disease, due to lack of inhibition of proteases, particularly neutrophil elastase.
- Key deficiency alleles are:
  - S (slow variant, 60% of wild-type expression)
  - Z (very slow variant, 10-15% of wild-type expression)
- Z variant is unable to leave hepatocytes; toxic accumulation damages hepatocytes and causes liver disease.

### α1-antitrypsin

- Gene on chromosome 14.
- Over 90 genetic variants described.
- Co-dominant inheritance with expression reflecting variants present.
- Expressed by hepatocytes and up-regulated 3-4 fold in acute phase response.
- Functions as a protease inhibitor, particularly important in inhibiting neutrophil elastase.

### Investigations:

1. Measuring serum **concentration of α1-antitrypsin**.
  - If borderline, consider checking phenotype.
  - If low, investigate phenotype.
2. Investigating **α1-antitrypsin phenotype** with isoelectric focussing (electrophoretic separation by pH).  
BUT:
  - Beware acute phase increasing low concs into normal range.
  - Always check phenotype in babies and infants, and in family studies.



Phenotype = P i M Z

α1-ANTITRYPSIN PHENOTYPING  
(Isoelectric focusing of serum samples, then immunoblot for α1-antitrypsin.)

### Causes:

There are many causes of hepatitis but the main causes are:

#### 1. Infection

→ check viral serology  
e.g. Hepatitis viruses  
HepB and HepC have been linked with mixed cryoglobulinaemia.  
e.g. others, such as CMV, EBV

#### 2. Autoimmune

- check liver autoantibodies
- Affects women more than men.
  - Type I autoimmune hepatitis is associated with antibodies to **smooth muscle antibodies** (80% sensitive) and **antinuclear antibodies**. Typically older patients.
  - Type II autoimmune hepatitis is associated with **antibodies to liver-kidney microsomes**, specifically cytochrome P450 2D6. Can affect younger patients and be a more aggressive disease.

#### 3. Alcohol (and drugs)

Remember that some drugs are hepatotoxic e.g. paracetamol, anticonvulsants.

### Liver autoantibodies

To see examples of staining patterns for antibodies to smooth muscle, liver-kidney microsomes, and other patterns, visit the website of the Clinical Immunology Department in Birmingham  
<http://medweb4.bham.ac.uk/websites/clinicalimmunology/index.asp>

## Autoimmune pancreatitis

Suggested association with raised IgG4 concentration but weak evidence and this is not a specific finding.

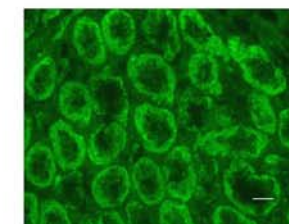
## Liver autoantibodies

Detected by indirect immunofluorescence on rodent composite sections of liver, stomach and kidney.

Includes antibodies to:

- **smooth muscle (SMA)**: target = filaments e.g. actin, vimentin, tubulin.
- **liver-kidney microsomes (LKM)**: target = cytochrome P450 2D6
- **mitochondria (AMA)**: target = E2 subunit of pyruvate dehydrogenase complex.
- **antinuclear antibodies (ANA)**: target = various (see also Rheumatology poster).

- SMA, LKM or ANA help indicate an autoimmune cause of hepatitis, but play no part in diagnostic criteria or monitoring or prognosis.
- There is no indication for repeat measurement.
- Positive autoantibody results can be NON-SPECIFIC e.g. SMA seen in viral infections.



Anti-mitochondrial antibodies: Speckled staining pattern in kidney tubules detected by indirect immunofluorescence.

## Primary Biliary Cirrhosis

### Laboratory findings:

1. Raised **alkaline phosphatase**
2. Raised **polyclonal IgM**
3. **Anti-mitochondrial antibodies** (95% sensitive)

BUT may need to check AMA subtype.

- Typically middle-aged women with pruritis, jaundice, arthralgia and fatigue.
- Untreatable, though ursodeoxycholic acid may help.
- May need liver transplant but disease likely to recur because still have autoantibodies.