Liver disease

Main topics to cover:
- Interpretation of LFTs
- Neonate with jaundice
- Child with jaundice
- Specific conditions: liver transplantation, Crigler-Najjar, hepatitis B & C, fatty liver

Interpretation of liver function tests
- Liver versus non hepatic sources
- Concept of intracellular versus membrane enzymes
- ALT vs AST
- GGT in obstruction/inducible
- Alkaline phosphatase
- Bilirubin conjugated versus unconjugated

ALT vs AST
- ALT
  - Highest concentration in liver
  - AST/ALT > 2 in alcohol, < 1 in fatty liver
- AST
  - Liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, WBC, RBC (decreasing order)
  - mitochondrial

GGT
- Single transmembrane ectoenzyme
- Inducible
- If obstruction ALP usually raised
- If induced, rest of LFTs usually normal

ALP
- Liver and bone
- Isoenzymes
- Transient hyperphosphatasemia
  - Usually > 5X ULN, child under 5, usually a viral infection, resolves in 3 months
**“non-liver” abnormal LFTS**

- Induced GGT
- Transient hyperphosphataemia
- Transaminases isolated
  - Coeliac disease
  - Muscle disorders

**Neonatal unconjugated hyperbilirubinaemia**

Is it
- Breast milk jaundice
- Haemolysis
- Something rare (e.g., Crigler-Najjar syndrome)?

**Bilirubin conjugation in the liver**

- Bilirubin is conjugated by Bilirubin Glucuronosyl Transferase (BUGT1)
- Excreted in conjugated (water soluble) form in bile

**Bilirubin UDP glucuronosyltransferase**

Sequencing of BUGT1
Identification of mutations
Clinical correlation

**Crigler Najjar Type I**

- Rare, autosomal recessive
- Unconjugated hyperbilirubinaemia
- Risk of kernicterus/death
- Complete lack of function of BUGT

**Prolonged breast milk jaundice**

“Prolonged Unconjugated Hyperbilirubinemia Associated With Breast Milk and Mutations of the Bilirubin Uridine Diphosphate-Glucuronosyltransferase Gene”

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Pediatrics 2000
Neonatal conjugated hyperbilirubinaemia

**Conjugated** (>15% abnormal)- main causes:
- Congenital *infection* eg TORCH, sepsis
- Structural: EHBA*, choledochal cyst
- Paucity syndromes eg Alagille/non-syndromic
- Metabolic: A1AT, CF, galactosaemia, Tyrosinaemia, HFI, Neiman-Pick A & C, Bile acid transport and synthetic disorders
- Endocrine: hypothyroid, hypopituitarism
- Neonatal hepatitis–“idiopathic”–getting smaller

EHBA
- Well baby, hepatomegaly
- Conjugated hyperbilirubinaemia
- Pale stools/LOOK YOURSELF
- Investigate (ultrasound, liver biopsy, HIDA scan) and treat by Kasai portoenterostomy
- Best results by 8 weeks of age bile drainage in about 60%
- Most will require liver transplantation

Neonatal liver disease

Idiopathic neonatal hepatitis–up to 25%
- Prognosis generally good
- Predictors of poor prognosis: jaundice>6months of age, acholic stools, persistent hepatomegaly, severe inflammation on biopsy, familial occurrence, low GGT
- If OK at 12months, long term outcome good with little evidence of liver disease

Hepatocyte transport systems

Bile acid transport disorders

For every transporter there is a disease!!

BYLER’S DISEASE
- chronic cholestasis & liver disease, normal GGT
- Mutation in FIC1 on 18q21
- P-type ATPase function unknown
- BRIC attacks of icterus and itch but no progressive liver disease
- Mutation also in FIC1? Why phenotypic heterogeneity
**PFIC II**
- Cholestasis, progressive liver disease, low GGT,
- Middle eastern, European
- BSEP/sPgp, 2q24 -homozygotes/ mainly compound heterozygotes
- Major ATP-dependent canalicular bile acid transporter, expressed only in liver, developmentally regulated (rat)
- Most PFIC II: spgp absent, decreased BA excretion

**PFIC III**
- Biliary cirrhosis, high GGT, portal hypertension, neonate to young adult, cholestasis of pregnancy
- Mutations in MDR3 gene causing inactivated truncated protein (homozygote or compound heterozygotes)
- MDR 3 - phosphatidylcholine translocation absence of micelle formation, causing bile duct damage (mouse model)
- UDCA/hepatocyte transplantation in mice

**Defects in Bile Acid Synthesis**

**Defects of Bile Acid Synthesis**

Pathophysiology:
- Abnormal bile acids can cause cholestasis by inhibition of BA transporters

Diagnosis:
- Primary vs secondary enzyme deficiency (e.g. severe liver disease)
- FAB-MS followed by GC-MS - frequency 2.5%

**Villin deficiency**

*Phillips MJ, Azuma T., Meredith SLM Lancet 2003*
Child with jaundice
- Gilberts syndrome
- Infections: EBV, HBV, (HCV)
- Drugs: paracetamol, erythromycin, flucloxacinill, NSAIDS
- Autoimmune-AIH, sclerosing cholangitis
- Metabolic-A1AT, Wilson’s, cystic fibrosis
- Structural-choledochal cyst, PSC

Hepatitis B-Natural history
- depends on age of acquisition, strain, genotype, gender, racial background, other health status
- if acquired in neonatal period, 95% becomes chronic
- "immunotolerant" phase eAG +, high levels DNA, almost normal ALT
- seroconversion at a rate of 5 to 15% per year- lower DNA, normal ALT, minimal abn on liver biopsy, reduced risk of HCC

Hepatitis B-Natural history II
- Some redevelop abn LFT with emergence of precore mutant –(eAG neg CHB)
- more aggressive, more common in Asia and Southern Europe (30 to 80%) vs northern Europe (10 to 40%)
- 25 to 40% of CHB die prematurely of liver disease or HCC
- Up to 1/3 children may have severe disease with significant fibrosis, even decompensated cirrhosis and HCC reported in childhood

HCV-natural history
- Adults
  - 20% cirrhosis in 20 years, 30% slower progression
  - 1-4% HCC per year in established cirrhosis
  - Worse with co-morbidity- eg HCV, HIV, alcohol, ?male gender

HCV-natural history
- Data in children:
  - 50 to 90% have persistently abnormal LFT's
  - 40 to 60% have RNA+ long term
  - majority mild hepatitis, but ?fibrosis common and progressive with time
  - Cirrhosis in 1-8%
  - ? Very slow progression if neonatal acquisition
Chronic liver failure
Liver transplantation routine hence aggressive management of chronic liver disease and its complications
- Nutrition-NG tube feeding/MCT formulas
- Bleeding-sclerotherapy/banding/B blockers/TIPS
- Osteoporosis- densitometry/vitamins/Ca, PO/bisphosphonates

NASH/Fatty liver/NAFLD
- NALFD-spectrum from fat alone, fat +inflammation(NASH) and cirrhosis
- NASH-obese, hypertriglyceridaemia(+/_ hypercholesterolaemia), insulin resistance
- Fatty liver on ultrasouns
- Mild ALT>AST
- Improve with weight loss

Treatments for liver failure
- NG nutrition
- Variceal banding

Paediatric TIPS

Liver transplantation
- Done in children in Melbourne, Sydney and Brisbane
- Commonest indication –EHBA
- Outcome: 86% long term survival
- Operation- cadaveric donor, left lobe cutdown or whole organ (8-18 hours)
Post-operative outpatient care

- Examination looking for infection (chest, skin, wounds), obstruction, drug side effects- BP, gums, hair, bones, PTLD
- Investigations: LFT, renal function, FBE, monitor immunosuppressive –FK 506, cyclosporin (trough levels)
- Medications

Liver transplantation-medication list

- Immunosuppressives: FK506 (tacrolimus), cyclosporine, azathioprine, prednisolone
- Antibacterial-bactrim
- Anti-fungal-nilstat
- Antiviral-acyclovir
- Antihypertensive-atenolol, captopril, nifedipine
- Supplements: Calcium, phosphate, magnesium, fat soluble vitamins, folic acid
- Bile drainage: ursodeoxycholic acid

Liver cell transplantation

What it is?

- Prepare a purified preparation of liver cells from a cadaveric organ.
- Inject liver cell suspension through the portal vein.
- Liver cells travel to liver, traverse sinusoids and “set up shop”
- Mouse models
- Human trials

The Hepatologists view….

Love your liver !!!!
Good Luck!!

I feel like such a failure. Whatever I do, something always goes terribly, terribly wrong.