Liver disease I/II

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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

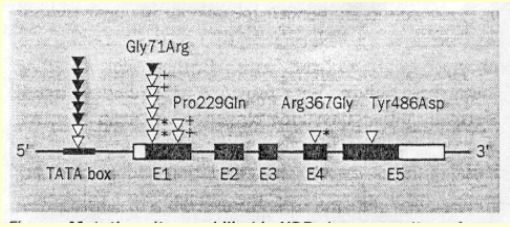
- Breast milk jaundice
- haemolysis
- something rare (eg Crigler-Najjar syndrome)?

Bilirubin conjugation in the liver

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

Sequencing of BUGT1
Identification of mutations
Clinical correlation

Bilirubin UDP glucuronosyltransferase



E1-E5 is exon 1 to 5, solid black are coding areas

Crigler Najjar Type I

- rare, auto 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"

Yoshihiro Maruo, MD, PhD*; Kashiro Nishizawa, MD, PhD§; Hiroshi Sato, PhEt@; Hiroko Sawa, MD*; and Morimi Shimada, MD, PhD'

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

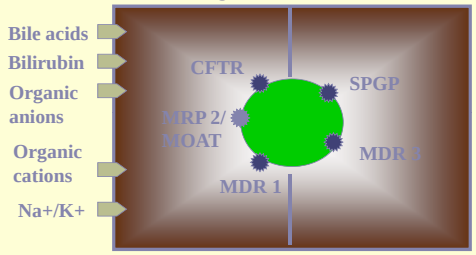
Idiopathic neonatal hepatitis–up to 25%

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!!

PFIC I

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

Bile Acid Synthesis: General Principals

- Cholesterol substrate, rate limiting step is 7α hydroxylase, changes to ABCD ring nucleus, side chain oxidation
- main and alternative pathways
- multiple cellular compartments
- **very complex!**

Defects of Bile Acid Synthesis

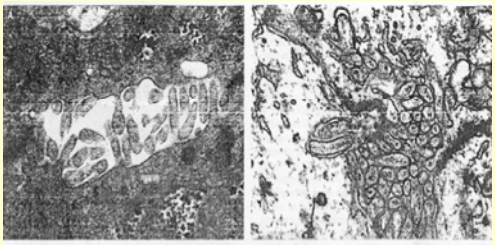
Pathophysiology:

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

Diagnosis:

- **Primary vs secondary enzyme deficiency(eg severe liver disease)**
- **FAB-MS followed by GC-MS - frequency 2.5%**

Villin deficiency

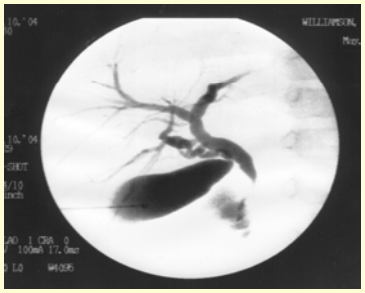


Phillips MJ, Azuma T., Meredith SLM Lancet 2003

Child with jaundice

- Gilberts syndrome
- Infections: EBV, HBV, (HCV)
- Drugs:paracetamol, erythromycin, flucloxacillin, NSAIDS
- Autoimmune-AIH, sclerosing cholangitis
- Metabolic-A1AT, Wilson's, cystic fibrosis
- Structural-choledochal cyst,PSC

Extrahepatic biliary obstruction



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

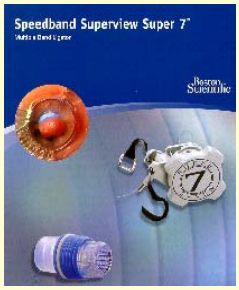
Liver transplantation routine hence aggressive management of chronic liver disease and its complications

- Nutrition-NG tube feeding/MCT formulas
- Bleeding-sclerotherapy/banding/B blockers/ TIPS
- Osteoporosis- densitometry/vitamins/Ca, PO/bisphosphanates

NASH/Fatty liver/NAFLD

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

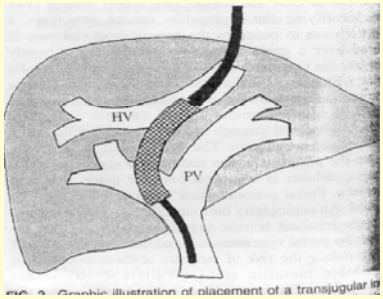
Treatments for liver failure



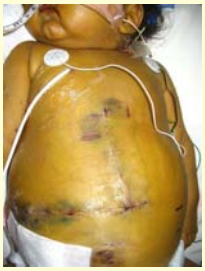
Variceal banding

NG nutrition

Paediatric TIPS



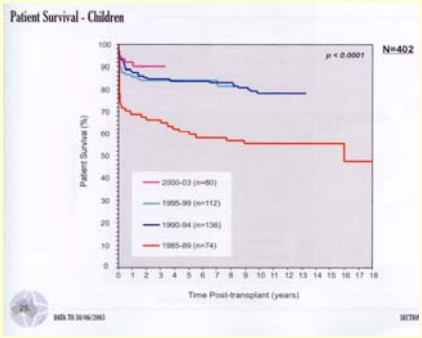
Liver transplantation



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)

Survival post-liver transplantation



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

- Immunosupressives: 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

Liver cell transplantation-mouse model

Rhim et al, *Science* 1994.

The Hepatologists view….

Love your liver !!!!

Good Luck!!


I feel like such a failure - whatever I do, something always goes terribly, terribly wrong
Willard