Liver disease in Infants

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Neonatal Hepatitis 1970-1990

N=1086

- BA/Obstructive: 36%
- Idiopathic: 31%
- Metabolic/Genetic: 18%
- Infective: 9%
- BD Hypoplasia: 6%

Neonatal Hepatitis 1992-2005
N=1625

- Idiopathic: 40%
- BA: 20%
- PNALD: 6%
- Alagille: 4%
- A1ATD: 11%
- PFIC: 5%
- Hypopituitarism: 2%
- Rare Metabolic: 2%
- Obstructive: 5%
- Caroli's: 1%
- Infective: 2%
- BD hypoplasia: 2%
Neonatal Cholestasis

~ 1:2700 live births
Infantile Cholestasis

Disease specific tests (about 30%)

- Metabolic
- Perinatal infections
- Endocrinopathies
- Choledochal cysts
- Others
Infantile Cholestasis

70% of patients no single test

- Biliary atresia
- Idiopathic neonatal hepatitis
- Alagille
- Others

Liver biopsy constitutes a major piece of ZIG SAW
Infantile Cholestasis

Aim of Investigations

- Identify Treatable Condition
- Recognise Complications
- Early Referral
Infantile Cholestasis
Clinical Clues

- Cutaneous haemangioma
- Liver
- Haemangioma

- Cystic mass
- Choledochal
cyst

- Micropenis
- SOD

- White hair
- HLH

- Ascites
- Spon.perf. of bile
  Storage
duct
disorder,
congenital heart, HLH,
hypothyroidism, Alpha-
1- anti trypsin def.
Infantile Cholestasis
Subsequent Investigations

- Alpha-1 antitrypsin phenotype
- Gal-1 phosphate uridyl transferase
- Urine succinyl acetone (delta amino laevulinic acid)
- Serum and urine amino acids
- Serum Cholesterol and triglycerides
- TSH/T4, Cortisol
- Sweat sodium/IRT/Mutational analysis for CF
- TORCH(S) screen
- Hep Bs Ag, hep C Ab, HIV Ab and other viruses
- x-ray long bones and spine
- MRI or CT scan of head
• babies with biliary atresia look normal!!
Infantile Cholestasis

Prelaparatomy diagnosis of biliary atresia

- Stool colour
- Ultrasound
- Hepatobiliary scintigraphy
- ERCP
- MRCP
- Duodenal aspiration
- Liver biopsy
prevalence of jaundice in UK

Incidence.
- 2 - 15% will remain jaundiced after 14 days.
- 0.2 - 0.4% will be conjugated.

1 in 17,000 live births will have biliary atresia

Biliary atresia

**Incidence**

1:14,000 - 1:21,000

Single commonest indication for LTx in children
Biliary atresia
1892
John Thompson - Edinburgh physician

Gallbladder
Bile Duct Remnants
JAPS

Classification

Type 3 (~90%)
Type 2 (~2%)
Type 1 (~8%)
Kasai’s operation - 1959

- Morio Kasai
- Surgery for “uncorrectable” (>80%) type of biliary atresia
Liver Transplantation - 1963
“Complementary & seamless”
Davenport et al. Lancet 2004

Current management

Early diagnosis - liver biopsy / ERCP

Kasai portoenterostomy

Liver transplantation

Overt cirrhosis
“maximally invasive surgery”
Biliary atresia
Kasai portoenterostomy

Successful

Unsuccessful
Biliary atresia

- Jaundice cleared
- Jaundice not cleared

Percentage survival

Tohoku Univ. Hospital (1971~1983)
Biliary atresia

jaundice cleared

jaundice not cleared

percentage survival

Tohoku Univ. Hospital
(1971~1983)
Infant Cholestasis

King’s Data n=1046

Biliary atresia

Cryptogenic hepatitis

Alpha-1 anti trypsin deficiency

Alagille syndrome

Choledochal cyst

Others

Total

1046
Infant Cholestasis

Giant cell hepatitis
Infant Cholestasis

Cryptogenic neonatal hepatitis

- complete resolution 80%
- progression to chronic liver disease 20%
Infant Cholestasis

Cryptogenic neonatal hepatitis

Indicators of poor prognosis

- positive family history
- parental consanguinity
- low γGT
- cirrhosis/severe fibrosis at presentation
Molecular genetics

Biochemistry
Low $\gamma$GT cholestatic liver disease

$= \text{failure of bile acid secretion}$

 ✓ 1º or 2º bile acid synthesis defects
 ✓ progressive familial intrahepatic cholestasis:

   - BSEP deficiency
   - FIC1 deficiency

29% not accounted for
Bile salt export pump (BSEP) deficiency

✓ *ABCB11* gene on chromosome 2q24-31
✓ function: major bile salt export pump
✓ exclusively hepatic phenotype

*presents with a neonatal hepatitis*
FIC1 deficiency

- ATP8B1 gene on chromosome 18q21
- Protein: P-type ATPase
- Function: aminophospholipid flipase?
- Hepatic and extrahepatic phenotype: malabsorption, pancreatitis, growth failure
Raised γGT cholestasis

- cholangitis / cholangiopathy
- primary inflammatory, weak genetic factors
- genetic
  - PSC, PBC, infective, biliary atresia
  - MDR3 deficiency (ABCB4)
  - North American Indian childhood cirrhosis
  - neonatal sclerosing cholangitis
General Management

- MCT rich formulae
- Vitamin K
- Vitamin A, E and D
- ? UCDA and other choleretic agents in selected patients
- Anti-pruritic agents and biliary diversion
- Transplantation
Paediatric Acute Liver Failure

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London
Acute liver failure in childhood

**Definition**

Multisystem disorder in which severe acute impairment of liver function (INR > 2) with or without encephalopathy occurs in association with hepatocellular necrosis in a patient with no recognised underlying chronic liver disease.
Pediatric ALF: Age of Onset

(N = 331)
Aetiology of ALF in children
KCH data
n=236 (1992-2004)
Neonatal Liver Failure

- Haemochromatosis
- HSV
- HLH
- Galactosaemia
- Tyrosinaemia
- OTC def
- Sepsis
- Paracetamol
- Hypocortisolism
Diagnostic difficulties

• Investigations aimed at-
  – Establishing the diagnosis
  – Exclude conditions not treatable by liver transplantation
Acute Liver Failure
Bone Marrow Exam

HLH

ALL

NPC

Pearson Syn

Syn
Value of liver biopsy??
Neonatal Haemochromatosis
Gestational alloimmune liver disease

- Severe liver disease of intrauterine onset associated with extrahepatic siderosis that spares reticuloendothelial system.
Neonatal Haemochromatosis

Gestational alloimmune liver disease

- Prenatal onset
- Rarely affects first born
- Highly recurrent in subsequent pregnancies
- Associated with maternal antibody to foetal liver antigen
High-dose immunoglobulin during pregnancy for recurrent neonatal haemochromatosis

Treatment of Neonatal Hemochromatosis with Exchange Transfusion and Intravenous Immunoglobulin

Elizabeth B. Rand, MD, Saul J. Karpen, MD, PhD, Susan Kelly, RN, Cara L. Mack, MD, J. Jeffrey Malatack, MD, Ronald J. Sokol, MD, and Peter F. Whittington, MD


Neonatal iron overload and tissue siderosis due to gestational alloimmune liver disease

Silvana Bonilla†, Joshua D. Prozialeck†, Padmini Malladi, Xiaomin Pan, Songtao Yu, Hector Melin-Aldana, Peter F. Whittington*

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Liver Dialysis
Auxiliary Liver Transplant

rationale
bridge to full recovery

Complete native liver recovery
Immunusuppression Free 76%
Hepatocyte Tx For ALF

- Synthetic and detoxifying function for few weeks
- No immunosuppression!
- Site that can be accessed in a coagulopathic patient
Hepatocytes in Beads
Equipment Hood in Aseptic Room
Cannulation
“Mincing” Digested Tissue
Repeated Washing and Centrifugation
Checking Cell No. and Viability
(Trypan Blue exclusion technique)
**Hepatocyte Encapsulation**

- Reaction vessel
- 250µm nozzle
- HCs/1.5% alginate
- 1.2% CaCl$_2$
- ~400-450µm Ø
CELL FUNCTION AND VIABILITY

MTT RESULTS OF MICROENCAPSULATED HEPATOCYTES CULTURED IN WILLIAM'S E MEDIA

UREA PRODUCTION OF ENCAPSULATED HEPATOCYTES CULTURED IN WILLIAM'S E MEDIA

FACTOR VII PRODUCTION OF ENCAPSULATED HEPATOCYTES CULTURED IN WILLIAM'S E MEDIA
Viability Testing of Encapsulated Hepatocytes Maintained in Ascitic Fluid

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 7</th>
<th>Day 14</th>
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<tbody>
<tr>
<td>Control</td>
<td>25%</td>
<td>50%</td>
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Culture medium only

Culture medium + ascitic fluid
Cell Viability

[Confocal Microscopy]
First in man Hepatocytes in Alginate beads for ALF March 2011
LIVER TREATMENT

Liver cells

Courtesy BBC
LIVER TREATMENT

Immune Cells

Courtesy BBC
Microbeads

Before Tx

Retrieved Microbeads

Albumin Production [Post-retrieval]

D1  D7  D14

Days in culture

Albumin (ng/mg protein)
Watch for new etiologies!