AN UNUSUAL CAUSE OF CHOLESTATIC JAUNDICE

UNIT II PEDIATRICS
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SPECIALITY
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Dr. Shobana (Dermatologist)
Dr. Rajenderan (Pathologist)
HISTORY

• Mast. R, 3 ½ Years old boy born to 2 degree consanguineous parents

PRESENTING COMPLAINTS

• Passing pale yellow colored sticky stools
• Progressive Itching/scratching all over the body
• Passing high colored urine
• Problems started since 3 months of age
• Diminished night vision- 1 year back
• No h/o fever, abdominal pain, jaundice
• No h/o involuntary movements, behaviour disturbances
• No h/o abdominal distension, haematemesis, melena, bleeding per rectum
• No h/o rash, joint pain
• No h/o joint swelling, prolonged bleeding
• No h/o abnormal swellings over the body
Treatment history

• Evaluated at 1 year of age by primary pediatrition: Baseline investigations, LFT, urine metabolic screening done showed values suggestive of cholestatic jaundice, Treated symptomatically

• At 2 years of age, presented to an ophthalmologist with complaints of diminished night vision diagnosed as Vit A deficiency and treated accordingly.
PERINATAL HISTORY

• No history suggestive of TORCH infection
• FTNVD, b.wt-3 kg
• No h/o neonatal jaundice, passed urine & stools normally.
Family and socioeconomic history

- No h/o suggestive of jaundice, bleeding disorders, gallstones disease, splenectomy

- Grade 3 lower middle class according modified Kuppusamy scale
General examination

- Conscious, oriented
- Icterus present, No clubbing / pedal edema / generalized lymphadenopathy
- No external markers of hypercholesterolemia
- No signs of liver cell failure
- **Head to foot examination**
  - No KF ring/abnormal facies/no evidence of vit A,D,E,K deficiency
  - Multiple scratch marks present all over the body with hyperpigmentation
## ANTHROPOMETRY

<table>
<thead>
<tr>
<th></th>
<th>OBSERVED</th>
<th>EXPECTED</th>
<th>%</th>
<th>PERCENTILES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>97 cm</td>
<td>101 cm</td>
<td>96</td>
<td>97</td>
</tr>
<tr>
<td>Weight</td>
<td>15.3 kg</td>
<td>16 kg</td>
<td>95</td>
<td>50-85</td>
</tr>
<tr>
<td>HC</td>
<td>47 cm</td>
<td>47-48 cm</td>
<td></td>
<td>3-15</td>
</tr>
<tr>
<td>MAC</td>
<td>16.5 cm</td>
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### VITALS:
- PR: 106/mt
- BP: 90/60mmhg
- RR: 24/min
- TEMP: 98.4’F
Pruritus marks
Icterus & lichenification
Pruritus
Systemic Examination

**UPPER GIT:**
- Lips, teeth, gums, cheek, tongue, tonsils, palate, oropharynx - normal

**LOWER GIT:**
- Liver palpable 3 cm below the right costal, firm consistency, Surface smooth.
- No splenomegaly

**OTHER SYSTEMS:** NORMAL
THOUGHTS AT THIS POINT!

- Neonatal hepatitis
- Inborn error of bile acid metabolism
- Hepatocellular cholestasis
Investigations

BLOOD ROUTINE

- HB 11 g/dl
- TC 14600 cumm
- Poly 5577 cumm
- Lymp 7927 cumm
- Eos 306 cumm
- Mono 773 cumm
- Baso 14 cumm
- PCV 33.7 %
- Platelets 1.84 lakhs/cumm
- ESR 51 mm/hr
• **LIVER FUNCTION TEST**

  • *Tests that measure detoxification or excretory functions*
    
    Serum bilirubin
    
    Total-2.6 mg/dl
    
    Direct-1.6 mg/dl

• **Serum enzymes that reflect damage to hepatocytes**
  
  SGOT – 78 U/L
  
  SGPT -90 U/L
• Serum enzymes that reflect cholestasis
  ALP -1355 U/L
  GGT -341 U/L (15-85 U/L)
• Tests that measure biosynthetic liver function
  Serum albumin -4.3g/dl
  Serum globulin -3.6 g/dl
• Coagulation profile
  PTT -26.7 (CONTROL 29.9)
  PT -15.5 (CONTROL 14.3)
  INR 1.09
• Plasma glucose-(fasting)-92 mg/dl (70-110)
• Ceruloplasmin-0.17 g/l (0.2-0.41)
• AB to HAV(IGM) NON REACTIVE
• HBsAg - NEGATIVE
• HCV - NON REACTIVE
**RENAL FUNCTION TEST**
- BUN: 11 mg/dl
- Creatinine: 0.4 mg/dl
- Electrolytes: N

**LIPID PROFILE**
- **CHOLESTEROL**: 216 mg/dl (0-200)
- Triglyceride: 126 mg/dl (0-150)
- HDL: 29 mg/dl (35-60)
- LDL: 180 mg/dl (0-100)
- **CHOLESTEROL/HDL ratio**: 7.5 (0-5 mg/dl)

**THYROID PROFILE** – N

**URINE ANALYSIS**: Bilirubin 2+

**USG ABDOMEN**: Hepatomegaly
COURSE IN THE HOSPITAL

• Started on antipruritic measures-UDCA. (No control). Hence started on Cholestyramine
• Also started on Vit-A,D,E,K & Calcium supplements
• Ophthal Evaluation done- No KF ring
• MGE opinion obtained-liver biopsy done under USG guidance
• Sample sent for histopathological evaluation
Preserved architecture
Feathery degeneration
Bile duct proliferation
FINAL DIAGNOSIS

• NON SYNDROMIC INTRAHEPATIC BILIARY CHOLESTASIS

PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS TYPE-3
DISCUSSION & LITERATURE REVIEW
• Definition
• Incidence
• Subtypes and characteristics
• HPE
• Prenatal Diagnosis
• Complications
• Management
• Approach to chronic cholestasis
• Conclusion
PFIC includes a heterogeneous group of autosomal recessive liver disorders characterized by impaired bile acid transport and excretion resulting in hepatocellular cholestasis; seen in the first few months of life with progression to liver failure. (by infancy to adolescence)
ABCB4 (MDR3 humans) 
(Mdr2 rodents)

Phosphatidylcholine floppase
PFIC3

TJP2
Tight junction integrity
Familial hypercholesterolaemia

ABCB11 (BSEP)
Bile salt pump
PFIC2

ATPB1 (FIC1)
Aminophospholipid flippase
PFIC1

Canalicular lumen
Primary bile

ABCC2 (MRP2)
Organic anion pump
Dubin–Johnson syndrome

ABCG5 + ABCG8
(sterolin 1 and 2)
Cholesterol floppase
Sitosterolaemia

CLDN1
Tight junction integrity
Familial hypercholesterolaemia

similar for a long time. Upon genetic distinction of the three
Incidence

• World wide 1 in 90,000 live births (*Pediatr transplantation* 2007;11:634-640)

• India: PFIC in NCS consensus report 1 in 1008 cases (*Indian Pediatrics* 2000)
PFIC-I & II

- First described in Amish family (BYLER)
- Neonatal onset - (mutation ATP8B1)
- Cholestatic symptoms (high sr. bile salts, bilirubin, transaminase, low GGT)
- Liver - fibrosis
- Extrahepatic symptoms (diarrhoea, pancreatitis, hearing problems)
- High sweat chloride concentration

(Text book of hepatology - Junn Rodes, Andres Blei, Jurg Reichen)
Liver transplantation resolves cholestatic phenotype
But extrahepatic symptoms remain
Chronic biliary diversion turns to be beneficial in both PFIC-I&II (Whittington et al 1994 J Pediatr Gastroenterol Nutr 18,134-141)
PFIC-I - liver specimen – canalicular lumen **Coarse granular bile**
PFIC-II- **Amorphous Bile**
PFIC-III

- Characterized by high GGT
- Associated with MDR3 (canalicular phospholipid transporter) deficiency due to mutations in ABCB4 gene.
- Production of highly detergent bile causes portal inflammation– bile duct proliferation--fibrosis
<table>
<thead>
<tr>
<th>CLINICAL FEATURES</th>
<th>PFIC-1</th>
<th>PFIC-2</th>
<th>PFIC-3</th>
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<tbody>
<tr>
<td>ONSET</td>
<td>NEW BORN</td>
<td>NEW BORN</td>
<td>LATE ONSET</td>
</tr>
<tr>
<td>JAUNDICE</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>PRURITIS</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>GROWTH RETARD</td>
<td>++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>FTT</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>CIRRHOSIS</td>
<td>1ST DECADE</td>
<td>1ST YR OF LIFE</td>
<td>YOUNG ADULTS</td>
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<tr>
<td>GALL STONES</td>
<td>+</td>
<td>MORE COMMON</td>
<td>+</td>
</tr>
<tr>
<td>epistaxis</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pancreatitis</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diarrhoea</td>
<td>++</td>
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PFIC-IV

- Defect in bile salt synthetic pathway
- HPE-intralobar cholestasis with giant cell transformation (interlobular bile ducts are usually spared)
- Low GGT
Complications

1. Fat soluble vitamin deficiencies esp: Rickets
2. Growth retardation
3. Diarrhoea: PFIC1
4. Pancreatitis: PFIC1
5. Cirrhosis with PHT: PFIC 2 & 3 >1
6. Hepatocellular carcinoma. PFIC2
Medical Management : Pruritus

- Neurogenic (due to centrally acting mediator which do not damage CNS)
  e.g., opioid peptides of cholestasis, morphine

- Medical management not very effective in PFIC
- Ursodeoxycholic acid: useful in PFIC 2 (10%), 30% in PFIC 3. (Jacquemin E Hepatology 1997)
- Rifampicin.
- Cholestyramine
- Phenobarbitone
## Treatments for hepatobiliary pruritus (Rooks text book of dermatology)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Level of preference</th>
<th>Level of effectiveness</th>
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</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>1</td>
<td>high</td>
</tr>
<tr>
<td>Opioid antagonists</td>
<td>1</td>
<td>high</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>2</td>
<td>high</td>
</tr>
<tr>
<td>Ursodeoxycholic acid</td>
<td>3</td>
<td>low</td>
</tr>
<tr>
<td>UVB phototherapy</td>
<td>3</td>
<td>low</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>3</td>
<td>low</td>
</tr>
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Surgical management

1. Partial External Biliary Diversion:
   - Decreases amount of BA in enterohepatic circulation by 50%
   - Decreases preload to canaliculus
   - Complete remission of symptoms--pruritus
   - Increases growth velocity
   - May delay the need for liver tx
   - Results best when there is mild fibrosis.

2. Illeal resection
Liver transplant

Only effective therapy with good outcome and minimal morbidity in patients with PFIC and cirrhosis.

Indication: Intractable pruritus and PFIC with ESLD
Chronic cholestasis

**Approach to chronic cholestasis**

**Chronic cholestasis**

- **GGT**
  - Low or N → Cholesterol
    - low → PFIC1,2
      - Liver bx
    - high → Inborn error of Bile acid metabolism, Familial hypercholanemia, Arthrogryposis-renal dysfunction cholestasis syndrome.
  - High → Dysmorphic facies
    - Yes → Alagille
      - Liver bx
    - No → PFIC 3
Prenatal diagnosis

- Reliable molecular antenatal diagnosis is available for PFIC$_1$, PFIC$_2$ and PFIC$_3$.
- Genomic DNA is isolated from Chorionic villus or cultured amniocyte samples.
- Done between 11th and 18th week of pregnancy.
- If Heterozygous pregnancy continued.

JPGN 2007;44;453-58
Conclusions

1. PFIC is an important familial cause of chronic cholestasis.
2. Surrogate markers such as $\gamma$GTP, cholesterol may be clue to diagnosis.
3. Partial biliary diversion is a good option for children with PFIC without cirrhosis.
4. Liver transplant is the final answer especially in PFIC 2 and 3.